The Journal of Thoracic Surgery

VOL. 30 JULY, 1955 No. 1

Original Communications

PERMANENT TOTAL BY-PASS OF THE PULMONIC VALVE

T. J. DONOVAN, M.D., AND J. F. DONOVAN, M.D.
BOSTON, MASS.

IN previous publications a technique was presented for circumventing the pulmonic valve.[1-5] The relevance of this research to the problems of congenital cyanosis was mentioned in these reports. Pulmonic stenosis and atresia—about 70 per cent of cases of cyanotic congenital heart disease—will present many pathological variants refractory to valvulotomy or the direct surgical approach. This is also true of the remaining 30 per cent comprising tricuspid atresia, truncus arteriosus, complete transposition, and other malformations. The technique described herein provides egress from the blocked cardiac chamber and is being applied with equal success to the right and left ventricles at the present time.[6]

As previously reported, a homologous vena cava was sutured end-to-side to the junction of left and main pulmonary arteries and affixed to a plastic tube which was inserted into the pulmonary conus of the right ventricle. The main pulmonary artery just distal to the valve was then totally occluded by ligature, thus diverting the entire cardiac output through this new pulmonary artery (Fig. 1). One year follow-up studies on this series of animals showed that the operative procedure was tolerated well, both immediately and remotely, and that the shunt closely simulated a valveless pulmonary artery.[5] Evidence was presented that the absence of a pulmonic valve over this one-year period seemed to have no significant untoward effect on cardiac function. This publication presents data on those animals studied three and one-half years postoperatively.

METHODS

Four of the 8 animals with main pulmonary artery ligation were sacrificed just over a year postoperatively (Group A), and the other 4, about three and

From the Laboratory for Surgical Research, Harvard Medical School, Boston, Mass.

This work was supported in part by grants from Winthrop Stearns, Inc., and The Upjohn Co.

Received for publication Nov. 10, 1954.

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

one-half years after operation (Group B). Both groups were run on the treadmill two to three months postoperatively, and those in Group B were given the same exercise again just before sacrifice. A few days after the first practice run on the treadmill, the duration of the second run was recorded at 4.5 miles per hour on a 10 degree incline. Other observations included pulse and respiratory rates, and duration of the recovery period.

Just before sacrifice, intravascular pressures were recorded under anesthesia with the open chest and intermittent insufflation of the lungs. Hamilton and Sanborn manometers were used in Groups A and B, respectively. Polyviso recording equipment was used in both groups.

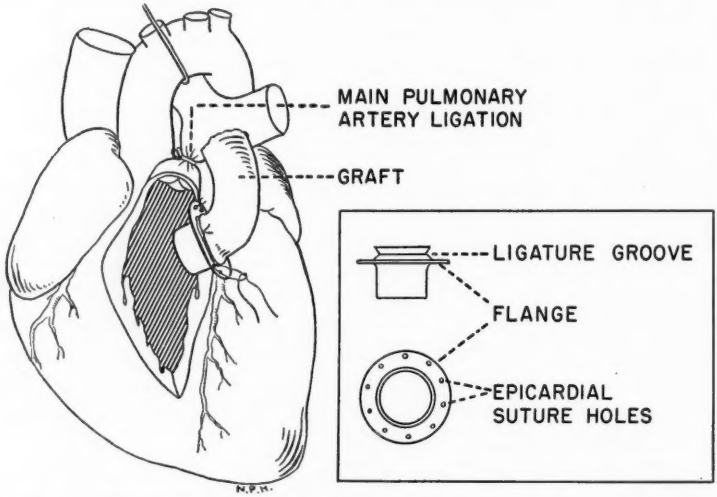


Fig. 1.—Diagram of extracardiac shunt with main pulmonary artery ligation.

RESULTS

Table I summarizes the data on a series of 12 animals. The two operative deaths were due to improper cardiotomy. The one postoperative death was due to rupture of a vein graft which was small and unevenly applied to the tube. The remaining 9 animals were well postoperatively. One of the 9 had a tube too short to reach the ventricle, and the main pulmonary artery was not ligated. Table II shows the treadmill results of the 8 animals with main pulmonary artery ligation.

Table III summarizes the physiological and anatomical data. Since cardiac outputs are not recorded, the pressure gradients across the shunts do not accurately quantitate the degree of stenosis. It is interesting, however, that the average gradient (excluding the dog with the aneurysm) was 4 mm. Hg, a low value even at basal cardiac outputs.[7] In no dog was there stenosis of the suture anastomosis. In one animal the stenosis was due to constriction of

TABLE I. RESULTS OF OPERATIVE SERIES

DOG	TUBE	POST-OPERATIVE DURATION IN MONTHS	CAUSE OF DEATH	CONDITION OF DOG	CONDITION OF SHUNT	REMARKS
19	Teflon	42.0	Sacrificed	Excellent	Patent	—
20	Teflon	14.3	Sacrificed	Excellent	Patent	Graft slightly small
21	Teflon	14.2	Sacrificed	Excellent	Occluded	Tube too short to reach ventricle
22	Lucite	0.5	Hemorrhage	Excellent before rupture	Patent ruptured	Graft uneven and small
23	—	Operative death	Ventricular fibrillation	—	—	Cardiotomy too large; poor resuscitation
24	Lucite	42.7	Sacrificed	Excellent	Patent aneurysm	Nutrition of donor poor; graft contaminated
26	Lucite	39.0	Sacrificed	Excellent	Patent	—
28	—	Operative death	Ventricular fibrillation	—	—	Cardiotomy too small; poor resuscitation
29	Lucite	13.4	Sacrificed	Excellent	Patent	Plaque caused stenosis
30	Lucite	13.3	Sacrificed	Excellent (mange)	Patent	—
31	Lucite	13.3	Sacrificed	Excellent	Patent	—
33	Lucite	42.0	Sacrificed	Excellent	Patent	—

the graft formed in preparation. In the others, however, it was uniformly located at the tube-vessel junction. The usual cause of the slight stenoses was the abrupt angulation of the graft at the tube-vessel junction. The average diastolic pressures in the right ventricle and pulmonary artery were 2 and 3 mm. Hg, respectively. The mean right atrial pressures averaged 4 mm. Hg or 2 mm. higher than the diastolic pressures in the right ventricle. The left atrial pressures in Group B averaged 5 mm. Hg or about 1 mm. Hg higher than the average right atrial pressures in Groups A and B.

Angiocardiography at six to eight months postoperatively demonstrated shunt patency in the 8 animals. Fig. 2 shows the typical anatomy of the new

TABLE II. TREADMILL RUNS AT 4.5 MILES PER HOUR ON TEN-DEGREE INCLINE

GROUP	DOG	POSTOPERATIVE DURATION	MINUTES ON TREADMILL
A	20	2.8 months	24
A	29	2.1 months	30
A	30	2.1 months	30
A	31	2.8 months	30
B	19	3.1 months	30
		3.6 years	32
B	24	2.3 months	30
		3.3 years	30
B	26	2.2 months	26
		3.3 years	25
B	33	3.5 years	25

TABLE III. SUMMARY OF ANATOMICAL AND PHYSIOLOGICAL STUDIES

GROUP	DOG	PRESSURES IN MM. Hg					HEART WEIGHT IN GM.	BODY WEIGHT IN KG.	ESTIMATED HYPERTROPHY RT. VENTRICLE	REMARKS
		MEAN R.V.	MEAN P.A.	GRADIENT	DIASTOLIC R.V.	DIASTOLIC P.A.				
A	20	12	9	3	0	0	176	16	++	Constriction of graft in preparation
A	29	13	9	4	2	3	167	15	+++	Plaque caused stenosis
A	30	15	11	4	0	2	147	15	+	—
A	31	13	12	1	2	?	155	14	++	Dog anoxic during pressure studies
B	19	19	16	3	4	4	135	16	+	Slight angulation and stenosis at stress area
B	24	36	20	16	0	3	191	16	+++	Aneurysm compressed graft at stress area
B	26	20	15	5	5	5	110	16	+	Slight angulation and stenosis at stress area
B	33	18	9	9	0	2	154	16	++	Slight angulation and stenosis at stress area

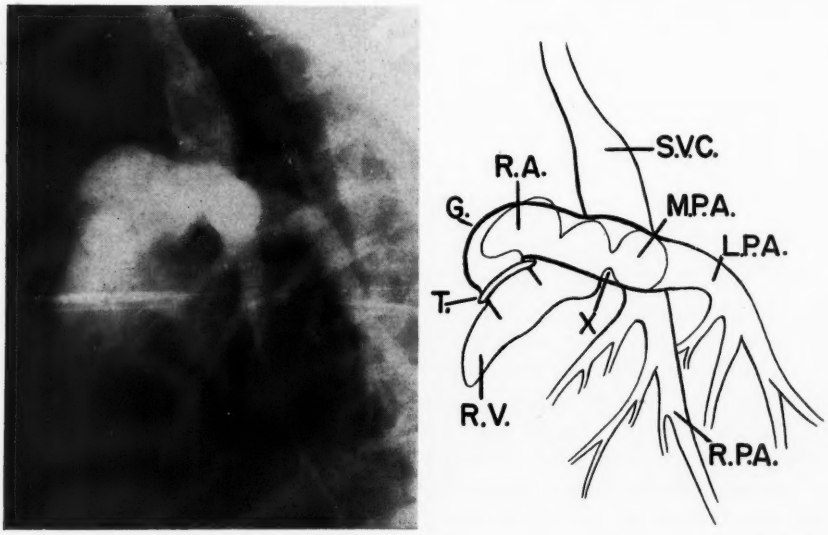


Fig. 2.—Diodrast angiocardiogram with explanatory diagram. In the latter *R.V.* denotes right ventricle; *T.*, tube; *G.*, graft; *R.A.*, right auricle; *X*, point of ligation; *S.V.C.*, superior vena cava; *M.P.A.*, main pulmonary artery; *L.P.A.* left pulmonary artery; *R.P.A.*, right pulmonary artery.

channel demonstrated radiographically. One animal (No. 24) had an aneurysm at the tube-vessel junction. The wall of the aneurysm was composed of healthy fibrous tissue and was partially lined with a thin clot. Despite 3 litters of pups and 3 runs on the treadmill, this aneurysm had not enlarged significantly or ruptured over the three-year period. It encroached on the lumen of the shunt, however, and caused the most marked stenosis and myocardial hypertrophy seen in these animals (Table III).

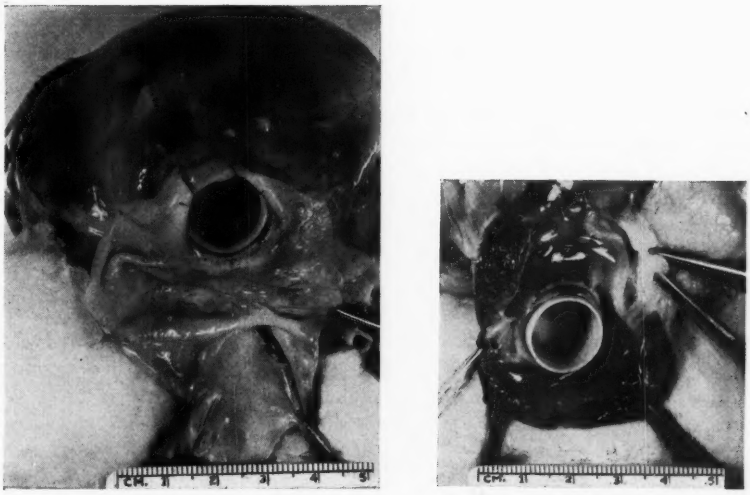


Fig. 3.—Epi- and endocardial views of the shunt one year postoperatively.

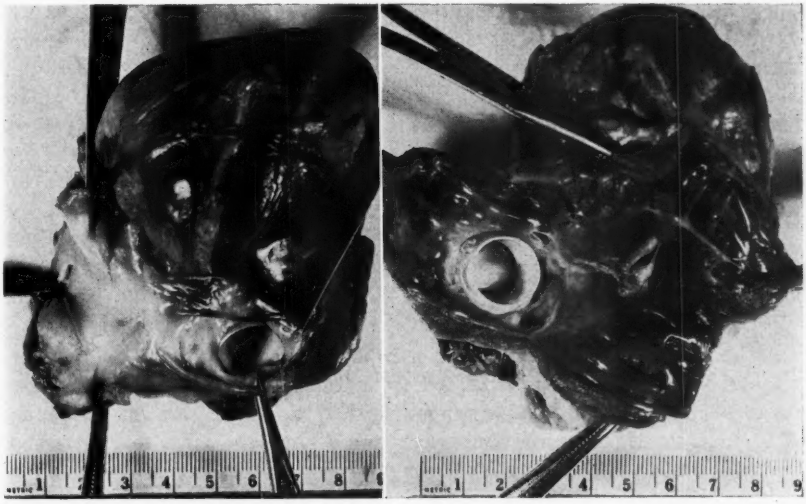


Fig. 4.—Epi- and endocardial view of the shunt three and one-half years postoperatively.

In 2 of the 8 animals there was a 1 to 2 mm. hole in the ligated main pulmonary artery which would just admit the tip of a probe. The volume flow through these channels could not have been of functional significance. As can be surmised from Fig. 2, most of the stroke volume is ejected against the portion of the graft opposite the epicardial mouth of the tube—henceforth referred to as the "stress area." Three of 4 in Group A had stress plaques in this area, wheras at three and one-half years postoperatively, only one animal had similar changes of minimal degree. Microscopically, these calcified plaques appeared cartilaginous in some sections. The early graft redundancy also disappeared in Group B, and the replacement fibrosis at the stress area caused a uniformly abrupt angulation at the epicardial mouth of the tube, which was the point of slight stenosis in the pressure studies. In 2 of the animals in Group A, a plaque appeared to project into the lumen of the vein at the juxta-cardiac portion of the tube-vessel junction where the graft was redundant. Figs. 3 and 4 show the typical one and three and one-half year shunts completely patent and completely diverting. The suture anastomoses and grafts were well endothelialized and contained healthy, cellular fibrous tissue. Note the smooth endocardial anastomoses.

DISCUSSION

The operative mortality is definitely reducible by our present technique. These decisive refinements in the endocardial anastomosis will be detailed in a later publication.

Although these dogs were not exercised on the treadmill preoperatively, experience with untrained normal dogs controls these observations. It is to be noted that their exercise tolerance did not decrease over a three-year period. Since the myocardial reserve is the important limiting factor in these runs, these data are a measure of the over-all cardiac function. The amount of work done by these animals is incompatible with any significant decrease in myocardial reserve. Furthermore, the right ventricular endiastolic and right atrial pressures are inconsistent with heart failure. Although the low diastolic pressures in the pulmonary artery evince pulmonic regurgitation, the normally low mean pulmonary-arterial pressures minimize the amount of pendulum blood in the right ventricle. The pulmonic insufficiency was probably a minor factor as compared with the stenoses of the stress area in causing the right ventricular hypertrophy recorded in Table III.[7]

The estimated myocardial hypertrophy correlates well with the heart-weight/body-weight ratios calculated from Table III. Three of the ratios in excess of Herrmann's normal range (0.0060 to 0.0099) are in the animals with moderate right ventricular hypertrophy from the most marked stenoses in these shunts. The average heart-weight/body-weight ratio in these 8 animals is just within the normal range as delineated by Herrmann and others.[7, 8] Moreover, the heart weights and the heart-weight/body-weight ratios do not increase over the three-year period in this admittedly small series of cases.*

*The average heart-weight/body-weight ratio in dogs is about twice that reported in human beings.[9]

Since these stenoses and other pathological lesions are almost uniformly confined to the area of the tube-vessel junction, new shunts are being constructed with homologous grafts of aortic arch in place of the vena caval homografts. Curved plastic tubes are also being used to sustain the direct force of each systolic ejection. These new techniques should obviate the early rupture and late stenoses in this stress area.

Since it seemed preferable a priori to have a valve in the shunt, studies were pursued on the fate of the valves of venous homografts. Fresh femoral-venous homografts containing one valve were sutured into gaps of divided abdominal aortas and left pulmonary arteries. It was noted that clots frequently formed in the sinuses distal to the valve cusps despite permanent patency of the grafts. After a few weeks the cusps adhered to the graft wall and failed to function. This process along with the host replacement fibrosis renders the valve in the venous homograft of little value for long-term

Fig. 5.—Successful by-pass of the aortic valve. Lucite ball valve in the apex of the left ventricle leads to thoracic aorta via an aortic homograft sutured end to side. Aorta proximal to this anastomosis is completely occluded.

function. Lucite ball valves have therefore been studied under systemic arterial pressures in shunts from the apex of the left ventricle to the side of the thoracic aorta. Fig. 5 shows a successful circumvention of the aortic valve.[5] Although in this shunt, performed in 1950, the ball valve wore out in five weeks, revision of the valve subsequently has largely eliminated this problem.

SUMMARY AND CONCLUSIONS

One- and three-year postoperative studies are reported on animals with permanent ligation of the main pulmonary artery and total by-pass of the pulmonic valve through an extracardiac shunt. The shunt of plastic tube and venous homograft connects the right ventricle to the main pulmonary artery just distal to the occlusive ligature. Despite the absence of a valve in the shunt, it is tolerated well, both immediately and remotely postoperatively, as adjudged

by the results of treadmill runs, intravascular pressure determinations, heart weights, and other studies. The relevance of this research to congenital cyanosis of cardiac origin is discussed.

Acknowledgment.—We are indebted to Drs. S. J. Sarnoff, E. Berglund, and A. C. Barger for the intravascular pressure studies.

REFERENCES

1. Donovan, T. J., and Zimmermann, B.: The Effect of Artificial Surfaces on Blood Coagulability With Special Reference to Polyethylene, Blood **4**: 1310, 1949.
2. Donovan, T. J.: The Uses of Plastic Tubes in the Reparative Surgery of Battle Injuries to Arteries With and Without Intra-Arterial Heparin Administration, Ann. Surg. **130**: 1024, 1949.
3. Donovan, T. J.: The Experimental Use of Homologous Vein Grafts to Circumvent the Pulmonic Valves, Surg., Gynec. & Obst. **90**: 204, 1950.
4. Donovan, T. J., Hufnagel, C. A., and Eastcott, H. H. G.: Techniques of Endocardial Anastomosis for Circumventing the Pulmonic Valve, J. THORACIC SURG. **23**: 348, 1952.
5. Donovan, T. J., Hufnagel, C. A., and Eastcott, H. H. G.: Permanent Ligation of the Main Pulmonary Artery, Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, November, 1951.
6. Donovan, T. J., and Sarnoff, S. J.: Apical-Aortic Anastomosis for the Relief of Aortic Stenosis, Circulation Research **2**: 381, 1954.
7. Barger, A. C., Roe, B. B., and Richardson, G. S.: Relation of Valvular Lesions and of Exercise to Auricular Pressure, Work Tolerance, and to Development of Chronic, Congestive Failure in Dogs, Am. J. Physiol. **169**: 384, 1952.
8. Herrmann, G. R.: Experimental Heart Disease, Am. Heart J. **1**: 213, 1925.
9. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**: 79, 1928.

QUANTITATIVE OBSERVATIONS DURING THE FREEZE-DRY PROCESSING OF ARTERIAL SEGMENTS

SIGMUND A. WESOLOWSKI, CAPTAIN, MC,* LESTER R. SAUVAGE, CAPTAIN, MC, AND ROGER D. PINC, M.S.
WASHINGTON, D. C.

FREEZE-DRIED arterial segments have been shown to be stable in storage for prolonged periods and to serve as acceptable blood conduits when used to bridge defects in major homologous arteries.[2, 3, 5, 13, 14, 17, 18, 19, 20] Various apparatuses are currently being used to free-dry arterial segments. We have compared the characteristics of three and are reporting the results herein. These results indicate that satisfactory freeze-dried arteries may be prepared by simple techniques using suitable manifold-type vacuum systems.

APPARATUS

Vacuum systems of the three following designs were studied: (1) The Cryostatic Doublet† system similar to that developed by Hufnagel[14] (Fig. 1). which consisted of a Cenco-Hypervac 4 mechanical vacuum pump, a length of rubber hose, oil diffusion pump, a metal connecting elbow, a cold vapor trap, and a series of paired specimen traps at the bottom of which specimen tubes bearing arterial segments were attached. The term "doublet" refers to a pair of joined specimen traps. A Philips (ionization) gauge measured the absolute pressure in the metal elbow connecting the diffusion pump to the cold trap. (2) A glass manifold and trap system (Fig. 2). This consisted of a Cenco-Hypervac 4 pump, a short length of rubber hose, a glass cold vapor trap, a glass manifold bearing three standard taper joints to which specimen tubes were attached, and an absolute pressure gauge connected to the glass manifold. For purposes of this report, this system is termed the glass manifold and trap. (3) A brass trap-manifold system (Fig. 3). This consisted of Cenco-Hypervac 4 pump connected by a short length of rubber hose to the glass outer portion of the vapor trap. The inner tube of the trap was an integral part of the brass manifold. The glass outer portion of the vapor trap was jointed to the manifold by means of a brass taper joint extended as the inner tube of the trap.

Combinations of these systems were also studied. The combinations involved placing a doublet in series with brass manifold extensions with and without the use of the diffusion pump in series with the mechanical pump.

From the Division of Surgery, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington 25, D. C.
Received for publication Nov. 15, 1954.
*Present Address: Department of Surgery, State University of New York College of Medicine at New York City, 451 Clarkson Avenue, Brooklyn, N. Y.
†Manufactured by BiVac, 4001 Morrison Street, N.W., Washington, D. C.

Also, we studied systems in parallel off the mechanical pump to insure identical ambient conditions in certain comparison runs. The study of parallel systems was valid because the cold traps prevented cross-over of water vapors from one system to the other. The details of these in-series and in-parallel circuits will be described in the appropriate sections.

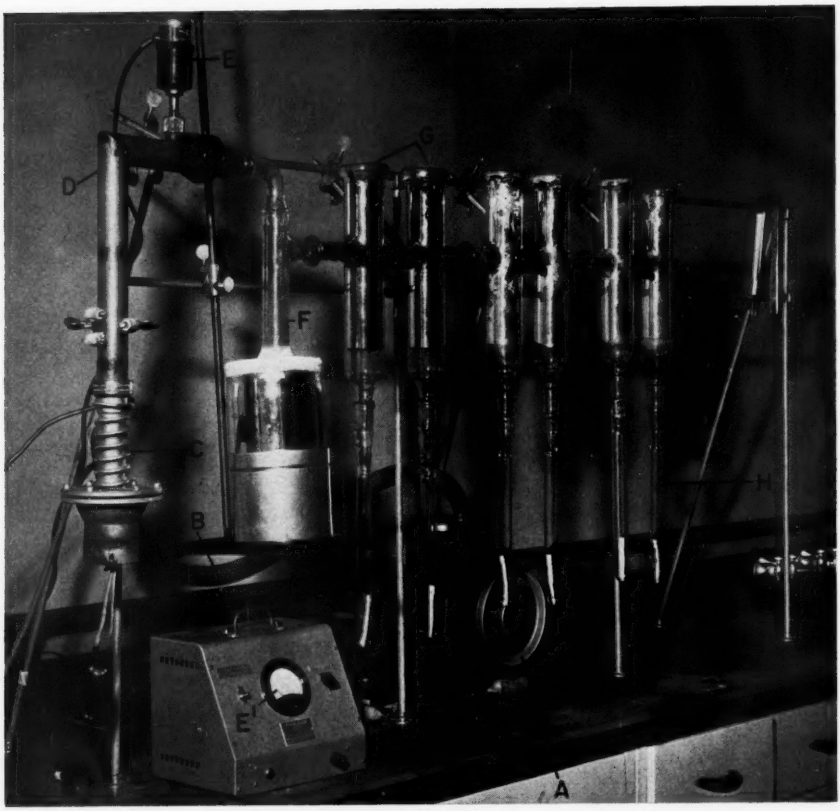


Fig. 1.—Photograph of the Cryostatic Doublet freeze-dryer. *A*, Cenco-Hypervac 4 mechanical vacuum pump. *B*, One-half inch inside diameter rubber hose leading to *C*, Cenco oil diffusion pump. *D*, Metal connecting tube. *E E'*, Philips gauge and indicator. *F*, Glass trap surrounded by Dewar flask filled with coolant (dry ice or liquid nitrogen). *G*, Doublet specimen traps. *H*, Specimen tube containing processing arterial segment.

McLeod, Philips, and Pirani vacuum gauges were employed in this study. The McLeod gauge had a range of from 1 to 5,000 microns of mercury absolute pressure. The Philips gauge had a range of measurement from 1/1,000 to 1 micron of mercury absolute pressure. The Philips gauge in the Cryostatic Doublet system described yielded no information as regards the water vapor pressures during the drying cycle because of its location between the cold vapor trap and the diffusion pump. However, this gauge did indicate the

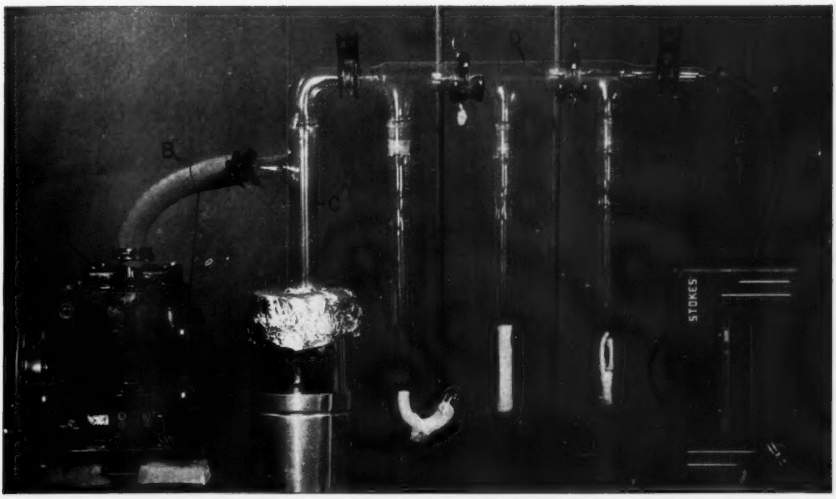


Fig. 2.—Photograph of the glass manifold and trap freeze-dryer. *A*, Cenco-Hypervac 4 mechanical vacuum pump. *B*, Rubber connecting hose. *C*, Glass trap surrounded by a Dewar flask filled with coolant. *D*, Glass manifold (Pyrex tubing, 1½ inches inside diameter, 17 inches long). *E*, McLeod gauge and indicator. *F*, Specimen tube containing human aortic segment.

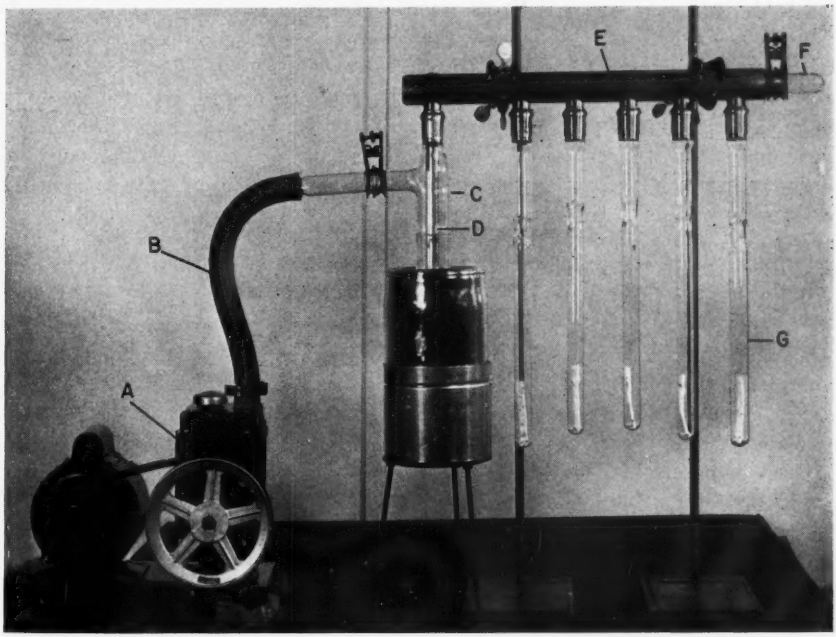


Fig. 3.—Photograph of the brass trap-manifold freeze-dryer. *A*, Cenco-Hypervac 4 mechanical vacuum pump. *B*, Rubber connecting hose. *C*, Glass outer tube of the vapor trap surrounded by a Dewar flask containing coolant. *D*, Brass inner tube of the vapor trap which is permanently attached to the end of a standard taper joint on the manifold. *E*, Brass manifold. *F*, Capped end of manifold. *G*, Specimen tube. The capped end of the manifold can be used as the attachment site of one of various gauges for the measurement of the vapor pressure during processing.

degree of evacuation of noncondensable gases (air) from the system. The Pirani gauge had a range of from 1 to 1,000 microns of mercury. Pirani gauges were used to measure water vapor pressures at various sites within the manifolds and specimen tubes.

The principle of the Pirani gauge depends upon the cooling effects of gases upon a hot wire. The cooling effect for any particular gas varies with the concentration (pressure). With changes in temperature of a hot wire, there are changes in resistance. These changes in resistance are calibrated in a bridge circuit involving the use of a second standard Pirani gauge. The Pirani gauge pressures were constantly recorded during processing by means of direct ink writing recorders.* Various gases at equal absolute pressures cool the hot wire of the Pirani gauge in proportion to the coefficient of thermal conductivity which is a constant for a given gas and is inversely proportional to the molecular weight. Thus, if hydrogen, water vapor, air and argon, *each at 200 microns of mercury true pressure,* be measured by the same Pirani gauge, the gauge reading will be approximately 500 microns for hydrogen, 300 microns for water vapor, 200 microns for dry air, and 100 microns for argon.[1] Pirani gauges are calibrated using dry air and, therefore, when used to measure pressures of water vapor during freeze-drying will lead to readings that are falsely high as regards the true pressure. On the other hand, when ethylene oxide is used, the readings are falsely low since this gas has a molecular weight greater than that of argon. Ethylene oxide at a true pressure of 200 microns of mercury will result in a Pirani gauge reading below 100 microns of mercury pressure. When using these gauges, therefore, one must know the gas involved so that the Pirani gauge reading may be corrected to true pressure. The corrected gauge reading of vapors immediately surrounding a frozen specimen is a good index of the temperature of the specimen.

EXPERIMENTAL METHOD

Three types of arterial segments were used in the present study: the pig abdominal aorta from the renal arteries to the bifurcation, pig thoracic aorta, and the entire human aorta with attached iliac vessels.

All arterial segments were prepared in a standard manner, weighed to 0.1 mg. using a Fisher Gram-atic balance and then frozen in specimen tubes to the temperature of dry ice (–72° C.). While the arterial segments were being prepared, the vacuum system, with all ports plugged, was evacuated until a base line (constant) pressure was attained. At this point the vacuum pump was stopped, the plugs removed, the specimen tubes rapidly attached to the ports, and the pump restarted. Dry ice was maintained about the specimens until the pressure of the system approached the base line of the dry system. At this point the CO_2 was removed from around the specimen tubes and the drying cycle begun.

*Gauge manufactured by Consolidated Vacuum Corporation; recorder manufactured by Brown Instrument Company.

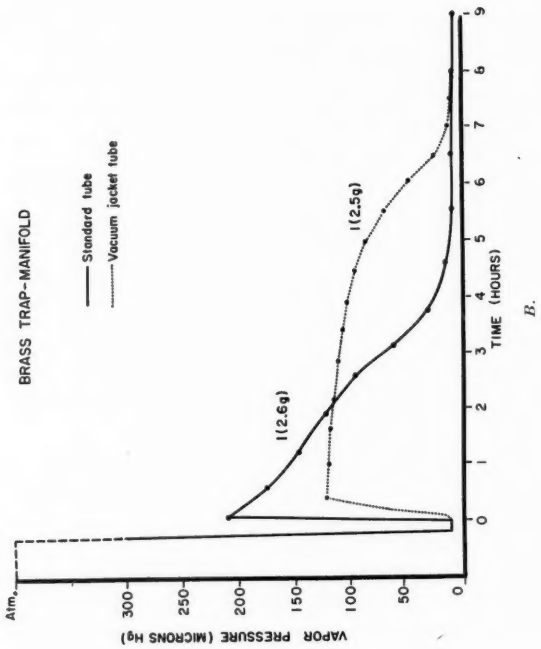
SUBLIMATION OF ICE

Before proceeding further, it is advisable to review briefly the physical principles involved in the drying of frozen arteries. Freeze-drying is the removal of water from a specimen by sublimation of ice under high vacuum. Simple evaporation of the water from an arterial segment in a vacuum system (without prior freezing) results in a specimen which has noticeably changed physical properties upon reconstitution and which, when homografted into the experimental pig, has an increased susceptibility to degenerative change and late thrombosis.[20] It is, therefore, advisable that arteries be kept frozen during processing.

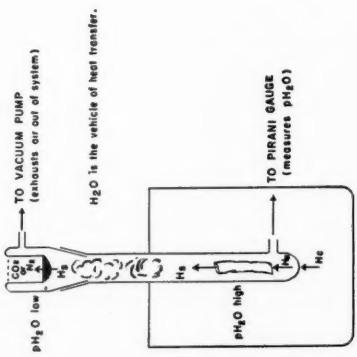
In order to illustrate the basic principles involved in sublimation of ice from frozen arterial specimens, a schematic freeze-dry system is shown in Fig. 4,*A*. The frozen artery is in a vacuum environment where its ice content is sublimed if the necessary heat is available from the environment. The vacuum environment must be maintained for the specimen to remain frozen. The vacuum is established and maintained by a mechanical vaccum pump. Since most commercial vacuum pumps do not work efficiently when pumping water vapor, a cold trap to desublime the water vapor, and thereby protect the pump, is included in the system. Since the rate of sublimation of ice from the specimen is inversely proportional to the total pressure within the system, the higher the vacuum attained and the less leaks in the system, the more rapid is sublimation. A perfect system with no external leaks or internal leaks of noncondensable gases could be sealed off from the mechanical pump once the vacuum had been established and sublimation would continue until the specimen was completely dry. In practice, however, the attainment of perfect systems is not possible, and, therefore, the mechanical pump must be kept in operation during the entire drying cycle.

At the bottom of the specimen tube shown in the schema is a side-arm to which can be attached a Pirani gauge. This gauge measures the total pressure of gases close to the specimen. When the air in the system has been evacuated to the base line pressure, we can consider that the magnitude of elevation above the base line pressure is solely the result of water vapor sublimed from the specimen during processing.

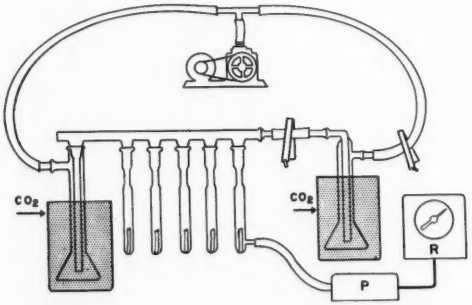
The ice in the specimen requires energy for the production of vapors (sublimation). This energy is supplied in the form of heat. Heat is conducted from the atmosphere at room temperature via the wall of the specimen tube to the specimen. One gram of ice requires 670 calories for sublimation. Sublimation results in the production of an area of greater pressure of water vapor surrounding the specimen with the establishment of a gradient from this greater pressure area to the area of lower pressure of water vapor surrounding the cold trap. Thus, the water vapor moves from the vicinity of the specimen to the cold trap where it is desublimed. This movement of water continues until there is a negligible amount of ice in the specimen, at which time it is dry.


BRASS TRAP-MANIFOLD
Standard tube
Vacuum jacket tube
I(2.6g)
I(2.5g)
VAPOR PRESSURE (MICRONS Hg)
Atm.
300
250
200
150
100
50
0
0
1
2
3
4
5
6
7
8
9
TIME (HOURS)

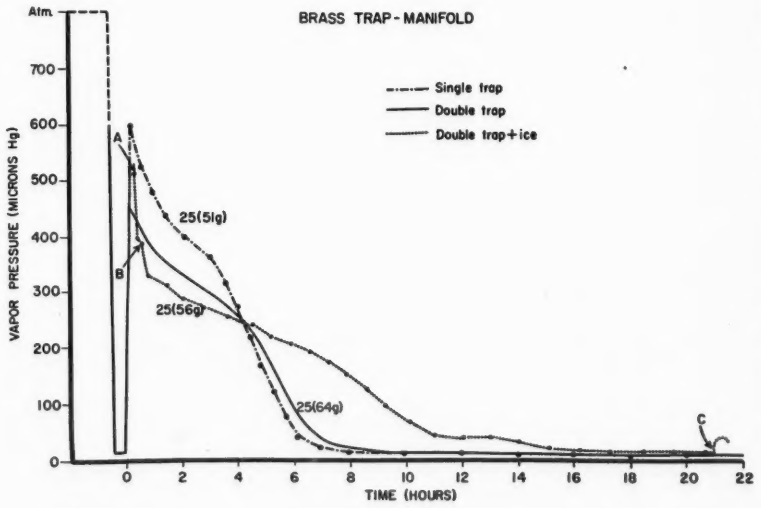
B.


TO VACUUM PUMP
(exhausts air out of system)
H_2O is the vehicle of heat transfer.
TO PIRANI GAUGE
(measures pH_2O)
pH_2O low
pH_2O high
CO_2
P_2O_5
H_2O
Hg

A.



C.



D.

Fig. 4.—Aids for demonstrating certain principles of the freeze-dry process. *A*, Schema of simplified freeze-drying apparatus. H_c, heat of conduction, H_r, heat of radiation, H_s, heat of sublimation, CO_2, dry ice or N_2, liquid nitrogen in cold vapor trap.

B, Uncorrected Pirani gauge readings plotted against time demonstrating the effect of partially heat-insulating the specimen tube.

C, Freeze-drying system for demonstrating effect of increasing cold trap surface.

D, Vapor pressure-time curves obtained using the apparatus in *C*. The numbers accompanying each curve represent the number of pig abdominal aortic segments used followed by the number, in parentheses, of grams of ice sublimed during the particular run.

The temperature of the specimen during this processing is governed by the equilibrium between the amount of heat supplied to and removed from the specimen. In the particular systems under consideration, the amount of heat supplied to the specimen is relatively constant since the specimen tube is exposed to essentially constant room temperature during processing. The amount of heat removed from the specimen is governed by the speed with which heat is removed from the specimen as heat of sublimation; this in turn depends directly upon the speed with which water vapor surrounding the specimen is evacuated. The speed with which the water vapor is evacuated depends upon the diameters of the conduits, the pressure of gases (air) in the system, the efficiency of the pump, and the temperature of the coolant in the vapor traps. In general, the more rapid the withdrawal of water vapor from around the specimen, the lower the temperature of the specimen.

Measurement of the peak pressure close to the specimen by means of a Pirani gauge is an acceptable index of the maximum temperature of the specimen during drying. The temperature of the specimen can be estimated by comparison of the *corrected* Pirani gauge reading with the standard vapor pressure-temperature curve for ice (International Critical Tables). As a general rule, if the *uncorrected* Pirani gauge pressure at no time exceeds 300 microns of mercury, the temperature of the specimen during processing does not exceed –30° C., so long as the specimen has a significant ice content.

That the heat from the ambient atmosphere influences the vapor pressure and drying time of the specimen was demonstrated with the brass trap-manifold system (Fig. 4,*B*). A single pig abdominal aorta was freeze-dried in a single standard tube and the vapor pressure measured in a side-arm at the bottom of the tube by means of a Pirani gauge. The vapor pressure drying curve is a solid black line in the graph. This experiment was repeated, but another single pig abdominal aorta was placed inside of a standard tube which was surrounded by a silver vacuum jacket intended to heat-insulate the specimen in the manner of a thermos bottle. It can be seen from the graph that the initial peak in vapor pressure was lower than that obtained by processing in a standard tube and that it took nearly twice as long to dry the specimen.

An experiment using the system shown in Fig. 4,*C* was performed in order to demonstrate that the amount of trap surface helps to prevent the occurrence of high initial vapor pressures. Two traps, one at each end of the brass trap-manifold were used. Dry ice-alcohol mixture was used as the coolant about the vapor traps. A rubber hose connecting the right end of the manifold to the trap on the right could be unclamped to include the benefit of the extra trap as desired. The results of this demonstration are summarized in Fig. 4,*D*. With a single (left) trap the peak vapor pressure during the processing of 25 pig abdominal aortas (using 5 aortas in each of 5 specimen tubes) was 600 microns; the pressure in the system returned to the base line in 10 hours. When two traps were used during the processing of another 25 pig abdominal aortas, the initial peak pressure was only 450 microns

of mercury, implying that the maximum drying temperature was lower than when a single trap was used. The vapor pressure returned to the base line in this run in the same time as when the single trap was used. However, in the latter run 64 Gm. of water were sublimed, whereas in the first run only 51 Gm. of water were sublimed. In a third run, using 25 pig abdominal aortas and a single trap, the initial vapor pressure was observed to be 510 microns of mercury. After five minutes of running, the second trap was allowed to function in the circuit (point A on Fig. 4,*D*) with an immediate drop of vapor pressure to 400 microns of mercury. The system was allowed to proceed for another 15 minutes. Cracked ice at 0° C. was placed about the specimen tubes (point B on Fig. 4,*D*) and maintained for a period of 20 hours. It is apparent

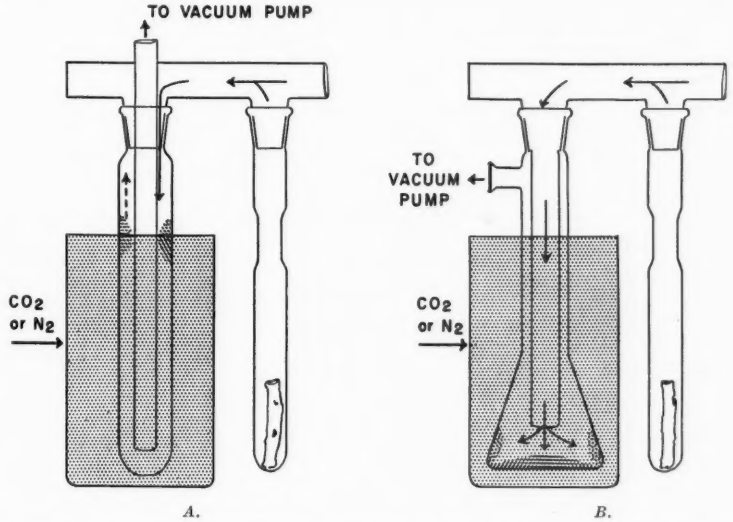


Fig. 5.—Drawings demonstrating the details of trap design. CO_2, dry ice, N_2, liquid nitrogen. Arrows depict the movement of the water vapors during processing. *A*, Improper design. *B*, Proper design.

from the vapor pressure curve of this run that the ice surrounding the specimen tubes delayed heat from entering the specimens and thereby delayed drying. With removal of the ice from about the tubes after 21 hours, a rise in vapor pressure occurred indicating that the specimens were not completely dry. (If dry ice at –72° C. had been maintained about the specimen tube, no drying of the specimen could occur since the vapor pressures in the vapor trap and about the specimen would be equal, resulting in a zero gradient of water vapor pressure.[6]

In considering the design of cold vapor traps, two factors must be kept in mind: (1) The trap must have sufficient capacity so that it can mechanically contain all the water in the form of ice that is to be removed from the specimen. Calculation of the amount of water contained can be easily done

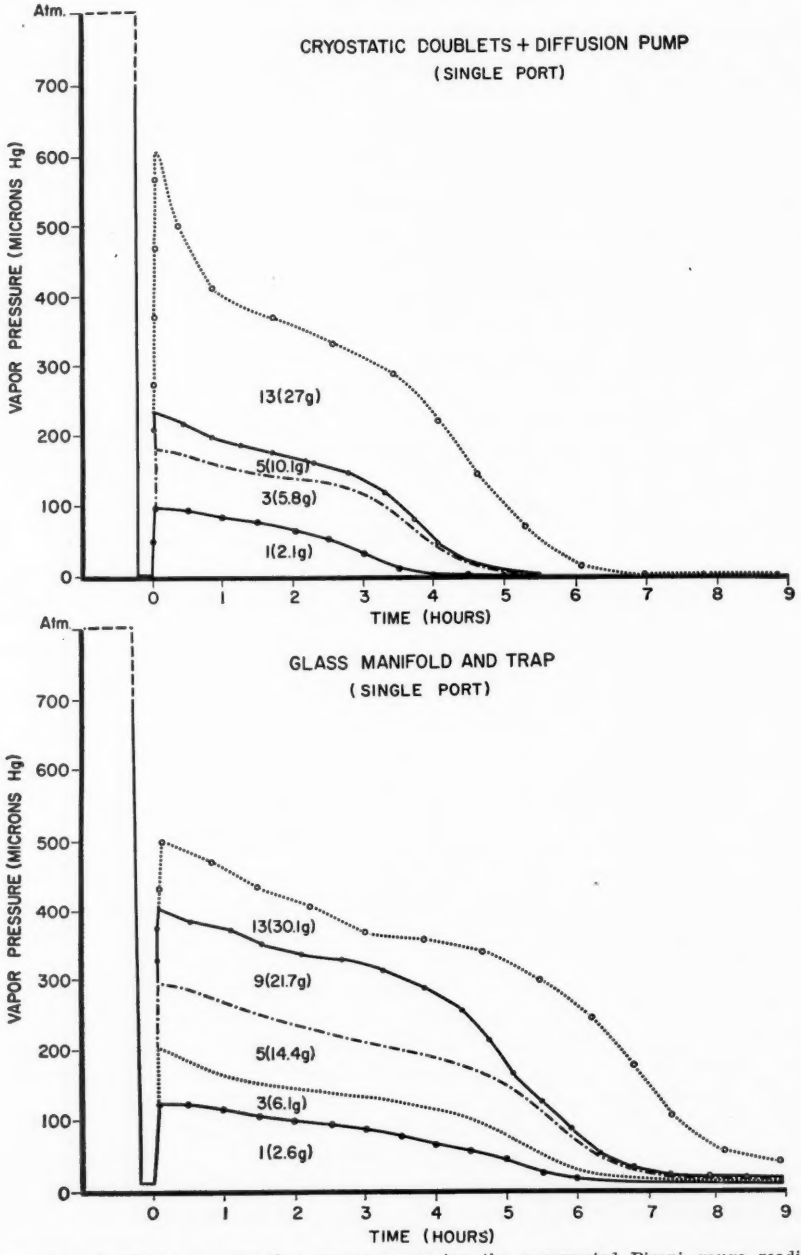


Fig. 6.—Vapor pressure-time curves comparing the uncorrected Pirani gauge readings in the Cryostatic Doublet and glass manifold and trap systems during the processing of various loads of pig abdominal aortic segments. Accompanying each curve are 2 numbers: the first represents the number of aortic segments used and the number in parentheses indicates the weight of ice sublimed from this particular load after processing to a final moisture content of 1 per cent or less.

since both human and pig arteries contain about 80 per cent of water, most of which is removed during the freeze-drying process. To increase the mechanical capacity of the cold vapor traps for our experiments, we have found it convenient to have the bottom of the cold vapor trap constructed of a 500 ml. Erlenmeyer flask, as illustrated in Fig. 5,*B*. (2) The trap itself should lead the vapors from the manifold system directly into the bottom of the trap where they can be desublimed. Proper design is illustrated in Fig. 5,*B*. Improper design is illustrated in Fig. 5,*A* where the vapor from the system is led into the trap external to the inner tube of the trap. Under the latter conditions the vapors condense at the level of the coolant that is used to surround the cold vapor trap. In such a design, especially when liquid

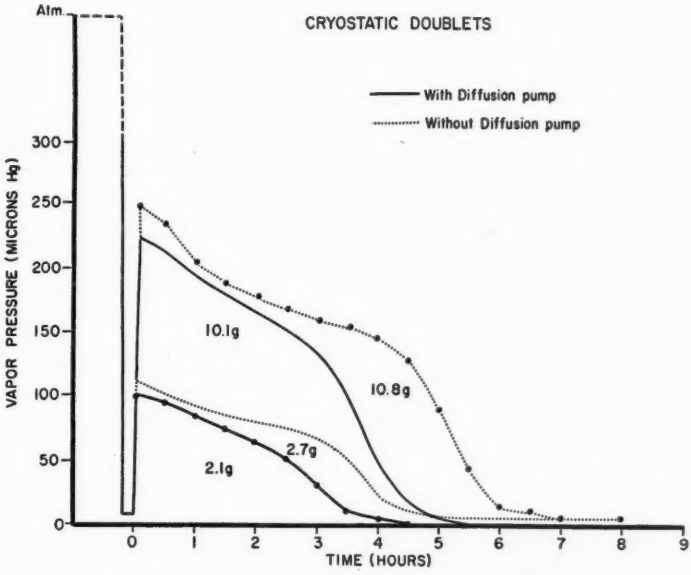


Fig. 7.—Graph comparing uncorrected Pirani gauge readings using the Cryostatic Doublet system with and without the diffusion pump. The number accompanying each graph indicates the grams of ice removed by complete processing of each load.

nitrogen is used, as the level of the coolant drops slightly, the condensed vapors resublime and feed vapors back into the system to interfere with the evacuation of water vapor from around the specimens. The design in Fig. 5,*B* necessitates that the coolant be nearly empty in the container surrounding the cold trap before any vapor feedback into the system can occur.

VAPOR PRESSURE STUDIES*

Continuous vapor pressures were measured at the specimen level by recording Pirani gauges during the entire drying cycle in the three basic systems described. Liquid nitrogen and dry ice-alcohol traps were used in the Cryostatic Doublet and glass manifold systems, respectively. In different runs,

*Uncorrected Pirani gauge readings are used in the graphs throughout this communication.

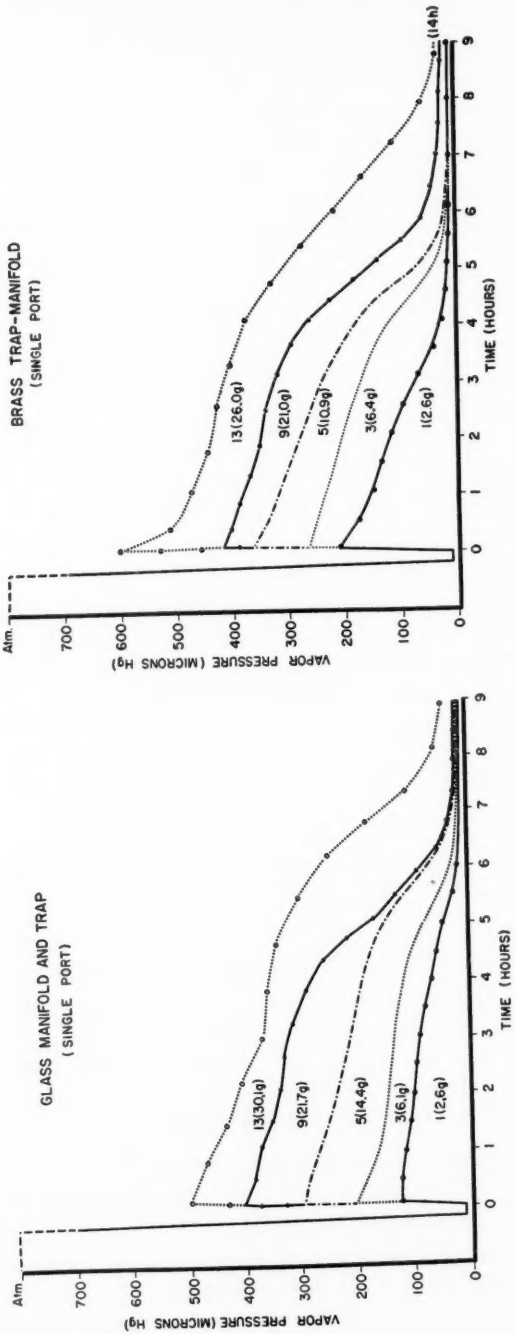


Fig. 8. *(For legend see opposite page.)*

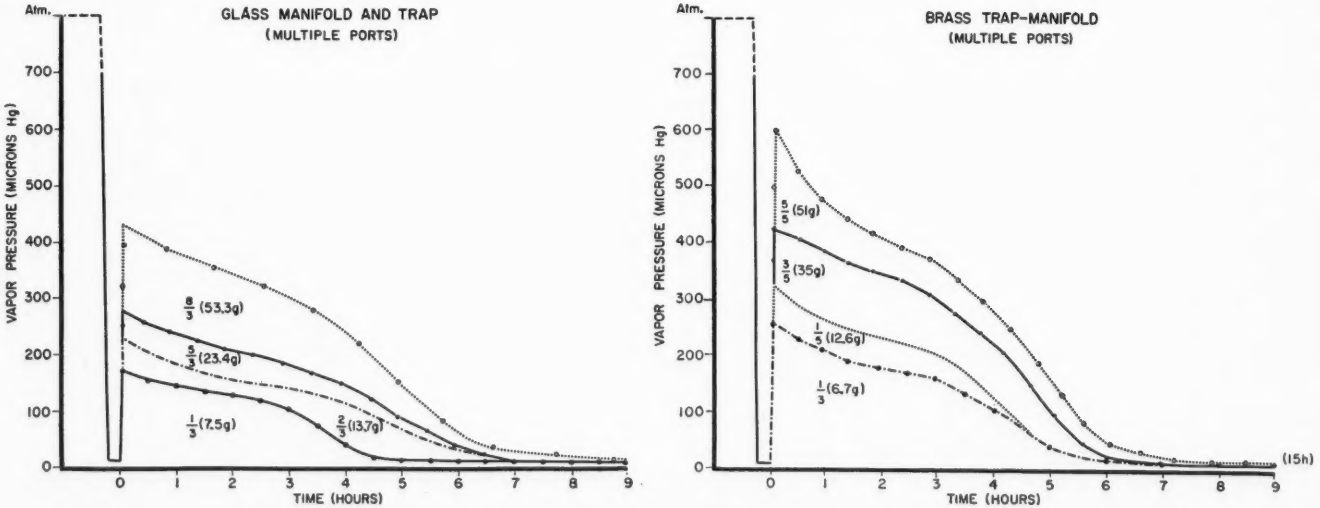


Fig. 8.—Uncorrected Pirani gauge readings obtained during the processing of various loads of pig abdominal aortic segments in a single specimen tube and in multiple specimen tubes using the glass manifold and trap and the brass trap-manifold systems. The numbers accompanying each curve in the "single port" graphs refer in sequence to the number of aortic segments used and the grams of ice, in parentheses, sublimed from these segments after reduction of the water content to 1 per cent or less. The numerator of the fraction accompanying each curve in the "multiple port" graphs indicates the number of aortic specimens in each tube (port) and the denominator indicates the number of tubes (ports) used. The parenthetical numbers indicate the grams of ice sublimed as above.

the number of pig abdominal aortas in a single tube was varied from one to thirteen. The results obtained in these runs are summarized in Fig. 6. For either system, the smaller the load, the shorter the drying cycle. Comparison of the two families of curves shows that for any given load of vessels the peak vapor pressure and drying time in the Cryostatic Doublet Diffusion pump system was generally less than that in the glass manifold and trap system. The load which corresponds to the maximum load that a single tube would be expected to carry in the freeze-drying of human vessels would be the curve referred to as 5 pig abdominal aortas (10 to 15 Gm. of water). The results of another experiment summarized in Fig. 7 demonstrate that it is probably the diffusion pump which makes the difference between the two systems. In this experiment the same Cryostatic Doublet was used to process two different loads. One load consisted of a single pig abdominal aorta which contained about 2 Gm. of water, and the other load consisted of three pig abdominal aortas, which contained approximately 10 Gm. of water. Each load was processed with and without the diffusion pump. As can be seen from the graph there was very little difference in the peak vapor pressure with and without the diffusion pump. However, after two hours in the 2 Gm. water load and after three hours in the 10 Gm. water load there was significant divergence of the vapor pressure curves, resulting in a demonstrated significantly shorter drying cycle when the diffusion pump was used. However, there was very little difference in the maximum temperature of the specimens during processing as evidenced by the peak vapor pressures. The vapor pressure curves obtained using the Cryostatic Doublet system without the diffusion pump are quite similar to those of the same loads using the glass manifold and trap system as illustrated in Fig. 6. Therefore, it is believed that the inclusion of a diffusion pump has the only advantage of shortening the drying cycle, but leads to no significantly safer temperature of the specimen during the processing.

Vapor pressure studies comparing the efficiency of the glass manifold and trap system with the brass trap-manifold system are summarized in Fig. 8. Dry ice-alcohol was used as the coolant about the traps in all runs that are plotted. In other runs the use of liquid nitrogen instead of dry ice-alcohol as the coolant did not influence the vapor-pressure curves. The graphs compare the vapor-pressure curves for varying loads on a single port in each system and also for varying the load on multiple ports in each system. In the single port studies, the tube was placed upon the port furthest from the cold trap and the vapor pressure measured in a side-arm at the bottom of the tube. In the multiple port studies, all ports were used and the vapor pressure measured in a side-arm at the bottom of the farthest from the cold trap. It is to be noted that for any given load in the single or multiple port graphs the initial vapor pressure attained in the glass manifold and trap system was slightly lower than that in the brass trap-manifold system, implying that the temperature for any given load was slightly lower in the glass manifold and trap system. However, the differences in drying temperatures were not significant. From comparison of the vapor-pressure curves, it can be seen that

for any given load of ice to be sublimed, the lower vapor pressures are attained if the load is divided into multiple specimen tubes. All three systems, that is, the Cryostatic Doublet system, the glass manifold and trap system, and the brass trap-manifold system, are adequate. The manifold systems, however, require slightly longer processing.

WEIGHT STUDIES

The reduction in water content as the drying cycle progressed was determined in each of the four systems illustrated in Fig. 9. These systems were: I. A series system of a mechanical pump, a diffusion pump, a cold vapor trap surrounded by liquid nitrogen coolant, one doublet, and two brass manifold extensions, each bearing six ports. Liquid nitrogen was used in the specimen trap of the doublet. II. The system is identical to that in I with the exception of deletion of the diffusion pump. III. The standard Cryostatic Doublet system as previously described, consisting of a mechanical pump, a diffusion pump, a cold trap, and three doublets in series. Liquid nitrogen was used in each of the specimen traps in the doublets and also as the coolant around the cold vapor trap. IV. The brass trap-manifold system, as previously described, with a brass extension bearing six extra ports. The results using either liquid nitrogen or carbon dioxide-alcohol mixture around the trap were identical in the latter system.

For the various runs, the number of tubes and the location of the specimen tubes were as indicated (Fig. 9). Standard pig abdominal aortas were used in these runs. In all but one run the load was constant: one pig abdominal aorta in each of four specimen tubes. However, in one run using System II, one doublet port and ten of the in-series manifold ports were used. Each tube in this case contained two arteries. These vessels dried along the same curve of percentage weight loss as those in runs involving only four tubes with one artery per tube.

Loss of water from the specimens with time was determined as follows: In System III the specimen tubes were sealed off at 1, 2, 4, 4½, 5, and subsequent hours after initiation of the process. In Systems I, II, and IV, the pump was stopped at intervals and the specimen tubes on each run were disconnected from the system; the specimens were weighed rapidly upon a Fisher Gram-atic balance to 0.1 mg. accuracy. The total time between interrupting a particular run and the weighing of the last specimen did not exceed six minutes. The specimens were then refrozen in a mixture of CO_2 and alcohol, placed back on the system, the system was re-evacuated, and the run was continued. The time of processing was corrected for the period of interruption. Following the last interruption for any particular run, the tubes were placed back on the system and the system was evacuated until the vapor pressure regained the level prior to the final interruption; at this point each tube was sealed off. All tubes were then stored.

The final moisture content was determined on 99 freeze-dried arterial segments by a modification of the technique of the National Institutes of Health.[11, 24] Ninety specimens were pig abdominal aorta segments and nine

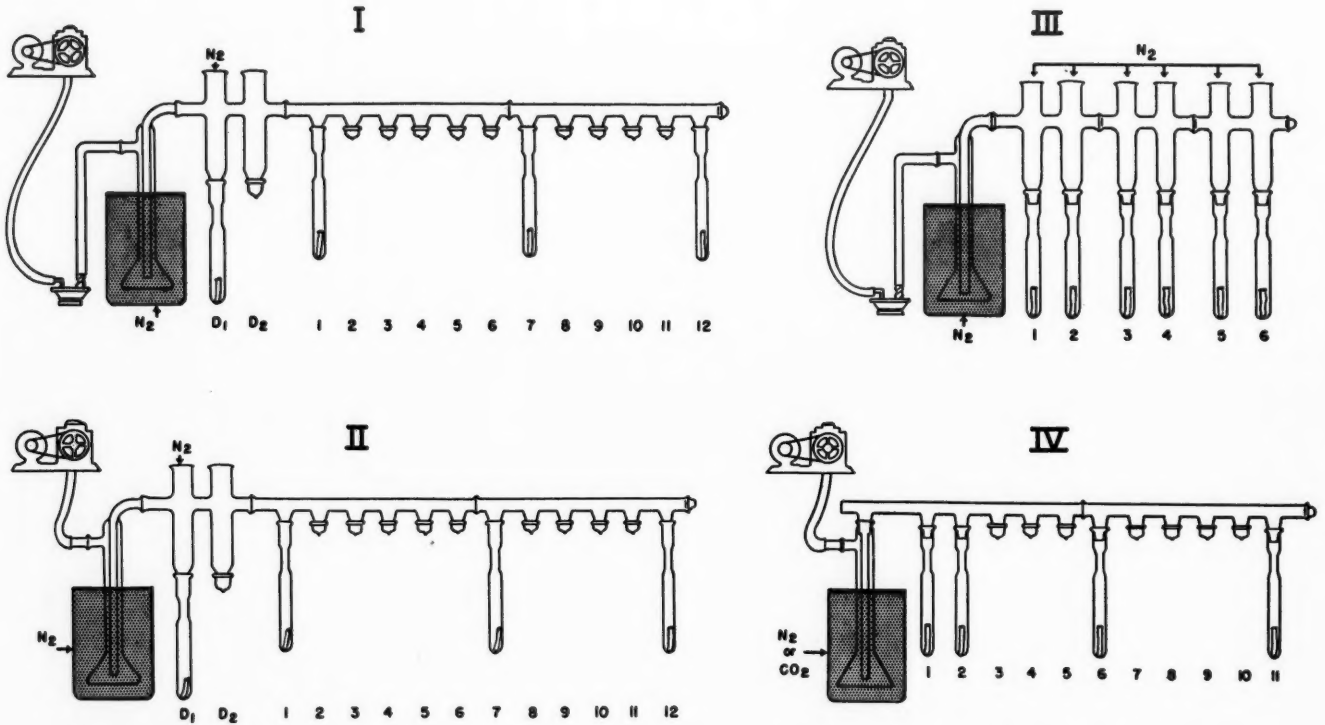


Fig. 9.—Schematic drawing of the four freeze-drying systems used to obtain the data in Fig. 10. (See text for details.)

were human aorta segments. No weighing bottles were used. The apparatus was housed in a large air-tight lucite box measuring 30 by 24 by 18 inches. A Fisher Gram-atic balance, capable of weighing grams to the fifth decimal place, and desiccator jars were contained within the box. Shoulder length rubber gloves were attached in air-tight manner to two ports at the front of the box. To secure a moisture-free atmosphere, large Petri dishes containing phosphorus pentoxide were placed in suitable locations within the box, and, during weighings, super-dry nitrogen was allowed to flow into the box at a rate of from 12 to 18 L. per minute. A small hole in the top was used to hand specimens into the box, and also to provide a vent for the super-dry nitrogen. In the conduction of the moisture determination, the specimen which was sealed in a glass tube in its primary vacuum, was removed after hot-wire fracture of the specimen tube. The specimen was quickly handed through the hole in the top of the box and was immediately weighed. It was then placed in a desiccator jar. At the bottom of the desiccator jar was a Petri dish filled with fresh phosphorus pentoxide. A stainless steel screen protected the top of the Petri dish. A stainless steel plate bearing numbered holes was suspended 1 inch above the screen. Each specimen was placed on end into a numbered hole. Thirteen to fifteen specimens were loaded into a single desiccator jar. The loaded desiccator jar was covered and evacuated to a pressure of 50 microns of mercury. At this point the desiccator jar was sealed. Forty-eight hours later the jar was opened and the specimens were re-weighed to determine water loss. They were replaced in the desiccator jar in early determinations and re-weighed at 96 hours. It was noted that there was no further loss in the second 48 hour period. Thus, in subsequent determinations, only one weighing was done at 72 or 96 hours. Four specimens were also sent to the National Institutes of Health for moisture determinations.* Their results were in very close agreement with ours.

Using the final weight of the moisture determination (after 72 to 96 hours of desiccation over fresh phosphorus pentoxide in a vacuum of 50 microns of mercury) as the dry weight (zero water content) of the artery, it was a simple matter to compute the weight of water per specimen at a given time of interruption by subtracting the final weight of the specimen from the observed weight of the specimen at the given time of interruption. This weight of water divided by the observed weight at the given time of interruption multiplied by 100 was taken as the water content of the specimen at this specific time. The water content was thus computed for each specimen at each interruption. Water contents were plotted against time for the various systems, I, II, III, IV. It was found that the initial water content of all arteries averaged 80 per cent (range from 75 to 83). Fig. 10 shows that there was remarkably little scatter in all observations and that the rate of water loss was approximately similar for the four different systems. The curves of Groups I and II were so similar as to be represented by a single line. Group III showed the most rapid weight loss of the four systems, reaching a moisture

*Conducted through the courtesy of Drs. G. Workman, T. F. Probey, and H. W. Burrows of the Biologics Control Laboratory, National Institutes of Health.

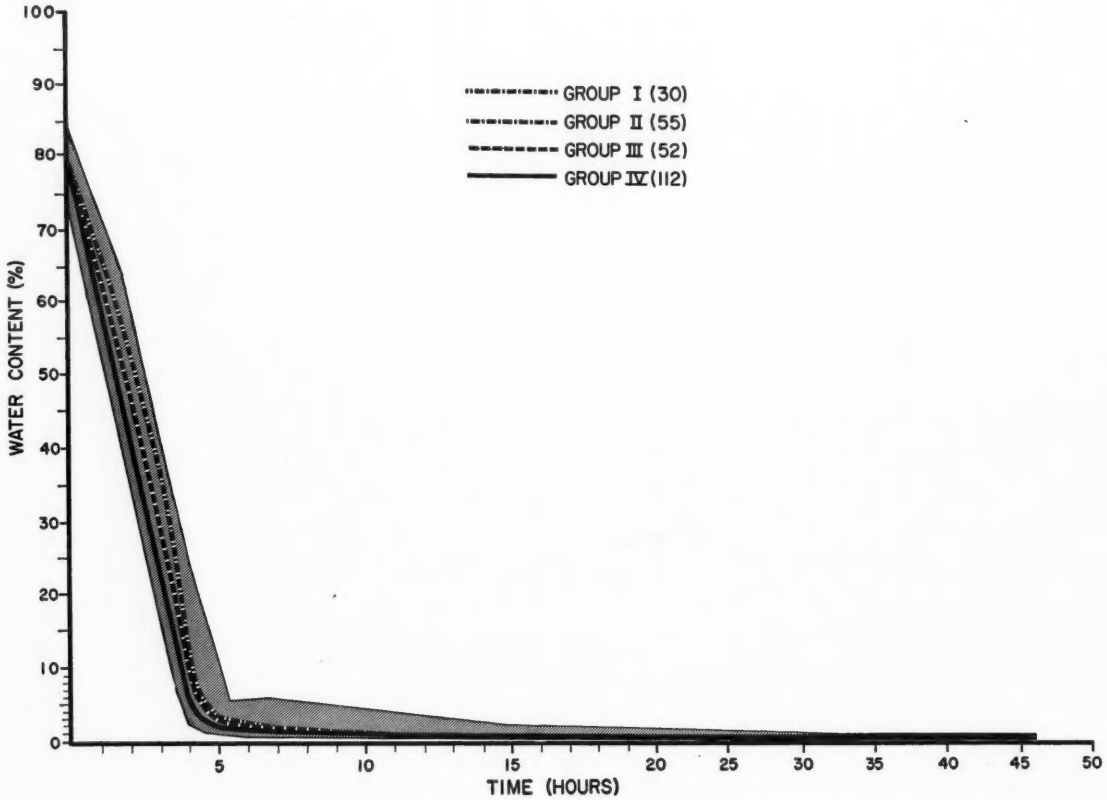


Fig. 10.—Graph comparing the rate of disappearance of the water (ice) content of pig abdominal aortas for the four different freeze-drying systems of Fig. 9. (See text for details.) The parenthetical numbers in the legends represent the number of determinations used to plot the curve for each group.

content of 1 per cent (removal of 99.75 per cent of original water content) after six hours of processing. In the other three groups the moisture content after 6 hours of processing was approximately 2 per cent (removal of 99.5 per cent of original water content), reaching the 1 per cent level at some time between 9 to 12 hours of processing. These times of reduction of the specimen to 1 per cent final moisture content are uniformly 1 to 2 hours longer than the time it takes the vapor pressure in these various systems to return to the base line pressure. In laboratory practice either the 6 hour or 12 hour time of processing is acceptable. In our opinion, exclusion of the diffusion pump for processing of reasonable loads on the systems described is justified because (1) its use does not significantly affect the drying temperature, and (2) its use involves significant added difficulties of procedure.

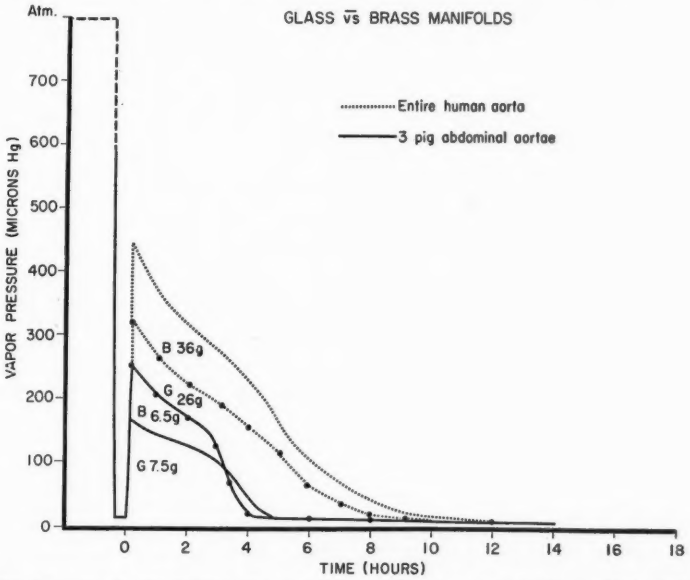


Fig. 11.—Graph illustrating the uncorrected Pirani gauge readings obtained during the processing of a standard load of three pig abdominal aortas and of a segmented human aorta and comparing the results when using the glass manifold and trap freeze-dryer *G*, and the brass trap-manifold freeze-dryer *B*.

Fig. 10.—Graph comparing the rate of disappearance of ice during the processing of the various drying systems of Fig. 9. (See text for details.) The parenthetical numbers in the legends represent the number to plot the curve for each group.

FREEZE-DRYING OF HUMAN VESSELS

Special studies were done during the processing of several human aortas. Fig. 11 summarizes the results of one of these experiments. On the plot the letter "B" refers to processing by the brass trap-manifold, and the letter "G," by the glass manifold. The numbers accompanying each graft represent the amount of water which was removed from the specimen during the processing. The two lower plots are the vapor-pressure curves obtained by the processing of three pig abdominal aortas, one in each of three specimen tubes. Vapor pressures were measured through a side-arm at the bottom of the tube farthest from the cold vapor trap. The vessels in both of these systems were processed

simultaneously, the glass and the brass systems having been in parallel to the mechanical pump. The two top curves in Fig. 11 summarize the vapor pressures during the processing of human aortas. For each system the entire human aorta was divided into three tubes as follows: The aortic arch was placed into a special arch tube,[20] the remainder of the thoracic aorta was placed into a straight tube, and the abdominal aorta and iliac vessels to the inguinal ligaments were placed as a single specimen into another straight tube. The aorta processed on the brass manifold was obtained at a routine autopsy and was relatively free of disease. The aorta processed in the glass manifold was sterile and subsequently banked. The tubes were attached to the ports so that the aortic bifurcation was in the tube farthest from the trap. Uncorrected peak vapor pressures for the glass and brass systems were 320 and 450 microns, respectively; estimated corrected values were approximately 225 and 300 microns, respectively. This implies that the maximum drying temperature of the specimens on the glass manifold was approximately –33° C. and that in the brass trap-manifold was approximately –30° C. The drying cycle was of approximately the same duration in both systems.

ETHYLENE OXIDE STUDIES

All data thus far presented were obtained using untreated arteries. The use of ethylene oxide for the sterilization of grafts as introduced by Hufnagel[14] is becoming more widely accepted. Its use increases the supply of human homograft material by permitting nonsterile procurement of specimens. Quantitative observations of the influence of ethylene-oxide-treated arterial segments upon the freeze-dry process were made.

A preliminary experiment with human aortas was done using two brass manifolds with dry-ice traps in parallel with the same mechanical pump. The aorta attached to one of the brass manifolds was treated with ethylene oxide as described by Hufnagel*; the aorta on the second brass manifold was untreated. A McLeod gauge was used to register the pressure at the end of each brass manifold. When processing was begun, it was noticed that the vapor pressure in both systems became greater than 3,000 microns of mercury and the specimens partially thawed. The reason that the pressure in the manifold bearing the untreated arteries rose to such a high level is that the ethylene oxide being removed from the treated specimens was not condensed at the temperature of the dry-ice trap, as the freezing point of ethylene oxide is –111° C. Maass and Boomer[16] demonstrated that ethylene oxide forms a chemical hydrate with a freezing point slightly above 0° C. Ethylene oxide hydrate is apparently unstable as a gas so that during the sublimation of the hydrate, ethylene oxide is liberated, necessitating condensing coolants at temperatures below –111° C. Liquid nitrogen (boiling point of –196° C.) is adequate as the coolant for this purpose.

A series of four experiments were then done to quantitate the effect of ethylene oxide treatment upon the vapor pressures during processing. In all

*Ethylene oxide kindly supplied by Dr. Charles Hufnagel, Georgetown University Medical Center.

of these experiments liquid nitrogen was used as the trap coolant. These experiments are summarized in Fig. 12. All experiments utilized the brass trap-manifold and a standard load of three pig abdominal aortas in a single specimen tube. Vapor pressures were recorded via a side-arm on the bottom of the specimen tube using the Pirani gauge and recorder. The vacuum system was pre-evacuated with all ports plugged and a base line reading of approximately 7 microns was noted in each experiment. The standard load in each of the four runs was frozen in a dry ice-alcohol mixture, attached to the end port of the brass trap-manifold and the specimen tube was surrounded by dry ice. The system was then re-evacuated. In the first experiment, no

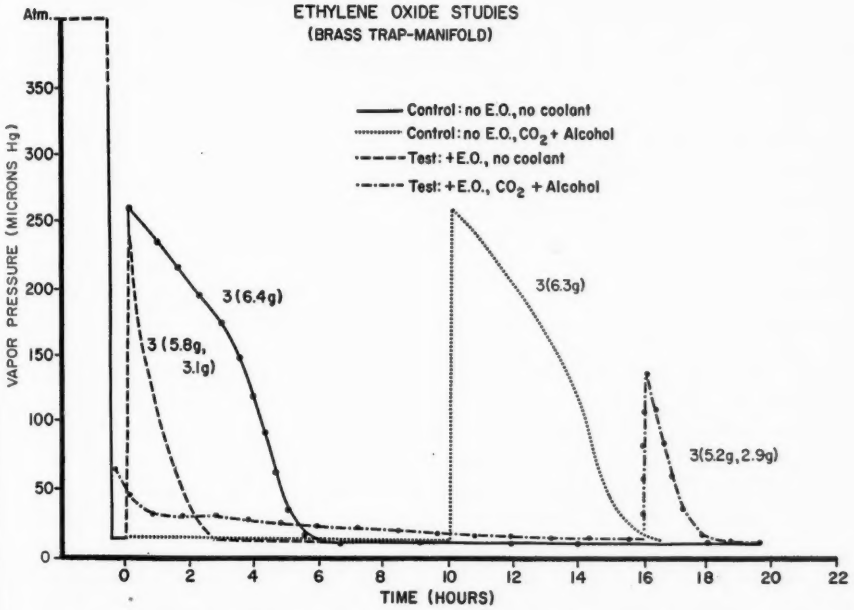


Fig. 12.—Graph summarizing the uncorrected Pirani gauge readings obtained during the freeze-drying of a standard load of three pig abdominal aortas under varying conditions of pretreatment. Accompanying the curves of control runs, the numbers in parentheses indicate the grams of ice removed during processing. The first parenthetical number accompanying the curve of each test run indicates the total grams of water removed from the load (initial weight minus final weight), and the second parenthetical number indicates the weight subsequent to ethylene oxide treatment. The difference between these two parenthetical numbers represents the amount of weight loss as the result of ethylene oxide treatment alone.

ethylene oxide treatment was done. The dry ice was kept about the specimen tube until the system was evacuated to its base line of 7 microns at which point the coolant was removed from around the specimen tube. There was a rapid rise of the vapor pressure to 270 microns of mercury. The vapor pressure then followed the expected decay cycle, reaching the base line of the system in approximately 7 hours. In the second experiment, no ethylene oxide was used but the CO_2 alcohol mixture was maintained about the specimen tube for a period of 10 hours. After 10 hours the carbon dioxide was

removed from around the specimen tube. The vapor pressure subsequently followed a pattern quite similar to that of the first experiment. In the third experiment the specimens were pretreated with ethylene oxide. As a result of the treatment with ethylene oxide, the specimen was found to lose 2.7 Gm. or approximately 50 per cent of its original weight. The dry ice was removed from around the specimen tube 3 minutes after the mechanical pump was started. The vapor pressure rose from 60 microns to 240 microns of mercury. The vapor pressure in this experiment was observed to follow an accelerated rate of decline, reaching the base line in approximately 5 hours. In the fourth experiment, the specimen was treated with ethylene oxide, and the dry ice was allowed to cool the specimen tube for 16 hours of processing. In contrast to the control, which was not treated with ethylene oxide and which was dry-iced for 10 hours, during this experiment the vapor pressure remained elevated above the base line. This implied that even with carbon dioxide and alcohol around the specimen tube, significant vapor pressure was exerted by the treated artery. After 16 hours of processing, the coolant was removed from around the specimen tube and there was noted a rapid rise in vapor pressure to the level of 135 microns of mercury. This demonstrated that the specimen was not completely evacuated of volatile materials (water, ethylene oxide and/or ethylene oxide hydrate). But the fact that the vapor pressure did not rise as high as in the noncooled ethylene-oxide-treated specimen indicates that during the 16 hours of cooling partial drying had occurred. It should be stressed that these vapor pressure readings are uncorrected Pirani gauge readings. Corrected readings imply that the untreated specimens had a maximum drying temperature of approximately –35° C. and that the ethylene-oxide-treated specimen without coolant had a maximum drying temperature of at least –26° C.

The results of experiments in which untreated human aortic segments were freeze-dried in parallel with ethylene-oxide-treated human aortic segments demonstrate that drying is accelerated in ethylene-oxide-treated vessels. After 15 hours of processing the untreated segments had a 1.5 per cent final moisture content whereas the ethylene-oxide-treated segments had a final moisture content of 0.3 per cent.

It is suggested that arteries sterilized by this method should be rapidly frozen immediately after the ethylene oxide is decanted, in order to prevent drying by evaporation with consequent protein denaturation.[20b]

BETA-PROPIOLACTONE STUDIES

There has been recent interest in the use of *B*-propiolactone as a sterilizing agent for human arterial segments to be used subsequently as grafts.[15] A 1 per cent solution is recommended. *B*-propiolactone is a relatively volatile liquid having a freezing point of –33° C.[21] A 1 per cent solution, however, has a freezing point close to 0° C. A group of 6 experiments using a standard load of pig thoracic aorta were performed. There were no differences in the vapor-pressure curves and duration of drying cycle during processing of the untreated and the

B-propiolactone-treated vessels. Dry-ice and liquid nitrogen traps were equally effective. The three systems (doublets, glass manifold, and brass manifold) were once again shown to be practical equivalents.

DISCUSSION

The critical temperature at which an artery must be maintained during sublimation is not known. For cytological work, Scott[22] has found that a temperature of –32.5° C. is practical. It has been shown that above the temperature of –20° C. ice crystals are indeed large and are destructive to the normal microscopic architecture of tissues, whereas ice crystals formed below –30° C. are much smaller and do not significantly distort architecture. Microscopic sections of pig abdominal aorta processed in this study at maximum temperatures of –30° C. and fixed in the dry state in formalin exhibit no significant architectural distortion. Further, it has been shown that blood vessels stored for prolonged periods in the frozen state at –27° C. are inferior when used as grafts to those which have been stored at –70° C.[4] Although no definite observations have been made as regards the critical drying temperature during the freeze-drying of arterial segments, one can say empirically that it is safe, if the temperature of the specimen does not rise above –30° C. until the specimen is nearly dry.

Ice crystals in the specimen can be large if the arterial segments are slowly frozen. Therefore, specimens should be quickly frozen prior to processing. Immersing the specimen within its tube in a mixture of dry ice and alcohol represents sufficiently rapid cooling.[14, 20, 25] Once the specimen in its tube is at the temperature of the dry ice-alcohol mixture (as evident by no further bubbling around the tube), it is attached to a port of a freeze-drying apparatus, the vacuum pump is begun, and the processing starts.

Sewell and Koth[23] suggest that arterial segments with final moisture contents of 5 per cent may prove more satisfactory upon grafting than segments dried to 1 per cent or less final moisture content. However, biological products (e.g., diphtheria antitoxin) with moisture contents of 5 to 8 per cent completely lose their potency after a few weeks of storage.[9] Flosdorf states: "In no case should a moisture above one per cent be allowed if the product is to be stored for more than a few months, particularly when not under refrigeration." Reduction of the moisture content of such sensitive physicochemical systems as plasma, egg albumin, and complement to less than 0.5 per cent results in no changes in electrophoretic pattern or immunologic activity after years of storage at room temperature.[10] Until definite proof to the contrary is presented, we assume that drying to a final moisture of 1 per cent or less leads to a biological product of optimal stability and minimal denaturation.

It is our opinion that the Cryostatic Doublet-diffusion pump system represents the ultimate in design for the freeze-drying of arterial segments, but that the manifold systems tested in the present study are easier to operate, less expensive, and practically as efficient.

For practical purposes an "overnight run" with average loads, using any one of the three systems described in this communication, will reduce the water content of arterial segments to 1 per cent or less. If measurement of the vapor pressure of the specimen side of the cold vapor trap is not feasible or if an individual is otherwise in doubt, a 24-hour period of processing should suffice. In loading specimens into tubes one must guard against jamming arteries into the bottom of the tube. If there is not space between the wall of the arterial segment and the wall of tube, at least along one side, there is danger of melting of the bottom of the specimen during processing. It is also advisable for vessels to be processed rounded rather than collapsed.

SUMMARY AND CONCLUSIONS

1. The principles of the freeze-drying have been reviewed.

2. Three variations in design of free-dry apparatus (Cryostatic Doublet-diffusion pump, glass manifold and trap, and brass trap-manifold systems) have been compared by quantitation of vapor pressure-time curves for various loads of adult pig abdominal aortas and human aortas. These systems with loads not exceeding 20 Gm. of ice per port are practical equivalents.

3. Data supporting the following conclusions have been presented:

a. The drying temperature of average loads (e.g., entire human aorta in three tubes) varies from –30° to –35° C.

b. The use of a dry ice-alcohol mixture (–72° C.) as the coolant about the vapor trap is as effective as liquid nitrogen (–196° C.) when processing untreated vessels. However, if ethylene oxide is used to sterilize the arteries, dry ice-alcohol is contraindicated as the trap coolant; liquid nitrogen is adequate in these circumstances.

c. The inclusion of a diffusion pump in the vacuum system shortens the drying cycle but does not significantly affect the drying temperature of arterial segments during processing. It is our opinion that an adequate mechanical pump alone is sufficient for practical laboratory processing.

4. Processing continued for 2 to 4 hours after the vapor pressure on the specimen side of the cold trap returns to the base line level results in arteries with a final moisture content of 1 per cent or less.

5. It is recommended that specimen tubes containing ethylene-oxide-treated vessels be kept surrounded by a dry ice-alcohol mixture during the first hour or two of processing. Treated vessels undergo some drying at –72° C. whereas untreated vessels exhibit no drying at –72° C.

6. Treatment of arterial segments with 1 per cent *B*-propiolactone prior to freeze-drying does not affect the vapor pressure-time curves during processing.

We are especially indebted to R. V. Gochenour, V.M.D., and E. W. Plischke, B.S., of the Biologic Research Department, Division of Immunology, Army Medical Service Graduate School, WRAMC, for lending us equipment, and for giving us valuable advice during experimentation and helpful criticism of our manuscript.

REFERENCES

1. Bachman, C. H.: Techniques in Experimental Electronics, New York, 1948, John Wiley & Sons, Inc., p. 39.
2. Brown, R. B., Hufnagel, C. A., Pate, S. W., and Strong, W. R.: Freeze-dried Arterial Homografts, Surg., Gynec. & Obst. **97**: 657-664, 1953.
3. DeBakey, M. D., and Cooley, D. A.: Surgical Considerations of Acquired Diseases of the Aorta, Ann. Surg. **139**: 763-777, 1954.
4. Deterling, R. A., Coleman, C. C., and Parshlet, M. S.: Experimental Studies of the Frozen Homologous Aortic Graft, Surgery **29**: 419-440, 1951.
5. Eastcott, H. H. G., Holt, L. B., Peacock, J. H., and Rob, C. G.: Preservation of Arterial Grafts by Freeze-drying, Lancet **1**: 1311-1314, 1954.
6. Flosdorf, E. W.: Freeze-drying, New York, 1949, Rheinhold Publishing Corp., p. 24.
7. Flosdorf, E. W.: Freeze-drying, New York, 1949, Rheinhold Publishing Corp., pp. 31-32.
8. Flosdorf, E. W.: Freeze-drying, New York, 1949, Rheinhold Publishing Corp., p. 42.
9. Flosdorf, E. W.: Freeze-drying, New York, 1949, Rheinhold Publishing Corp., pp. 47-48.
10. Flosdorf, E. W.: Freeze-drying, New York, 1949, Rheinhold Publishing Corp., pp. 138-142.
11. Flosdorf, E. W., and Webster, G. W.: The Determination of Residual Moisture in Dry Biological Substances, J. Biol. Chem. **121**: 353-359, 1937.
12. Hufnagel, C. A.: Section on Blood Vessels, Transplantation Bulletin **1**: 135, 1954.
13. Hufnagel, C. A., and Eastcott, H. G.: Homologous Arterial Grafts, Bull. Georgetown U. Center **4**: 119-123, 1951.
14. Hufnagel, C. A., Rabil, P. J., and Reed, L.: A Method for the Preservation of Arterial Homo- and Heterografts, Surgical Forum, 1953. Philadelphia, 1954, W. B. Saunders Company, pp. 162-168.
15. LoGrippo, G. A., Overhulse, P. R., and Szilagyi, D. E.: Procedure for the Sterilization of Contaminated Arterial Grafts With Betapropiolactane, Bacteriological Proceedings, 1954, p. 61.
16. Maass, O., and Boomer, E. H.: Vapor Densities at Low Pressure and Over an Extended Temperature Range. I. The Properties of Ethylene Oxide Compared to Oxygen Compounds of Similar Molecular Weight, J. Am. Chem. Soc. **44**: 1709-1728, 1922.
17. Marrangoni, A. G., and Cecchini, L. P.: Homotransplantation of Arterial Segments Preserved by the Freeze-dry Method. Ann. Surg., **134**: 977-983, 1951.
18. Pate, J. W., and Sawyer, P. N.: Freeze-dried Aortic Grafts, Am. J. Surg. **86**: 3-13, 1953.
19. Pate, J. W., Sawyer, P. N., Deterling, R. A., Blunt, J. W., and Parshley, M. S.: Early Results in the Experimental Use of Freeze-dried Arterial Grafts, Surgical Forum, 1952. Philadelphia, 1953, W. B. Saunders Company, pp. 147-151.
20. a. Sauvage, L. R., Wesolowski, S. A.: The Healing and Fate of Arterial Grafts, 1954. In preparation.
    b. Sauvage, L. R., Wesolowski, S. A., and Pine, R. D.: Freeze-dry Process for Arteries. In preparation.
21. Sax, I. N.: Handbook of Dangerous Materials, New York, 1951, Rheinhold Publishing Corp. p. 324.
22. Scott, G. H.: Personal Communication. Cited by Flosdorf,[6] p. 117.
23. Sewell, W. H., and Koth, D. R.: Section on Blood Vessels, Transplantation Bulletin **4**: 135-136, 1954.
24. U. S. Pharmacopaeia, XIV.
25. Wesolowski, S. A., and Sauvage, L. R.: Aortic Heterografts in Dogs, 1954. In preparation.

KARTAGENER'S SYNDROME: REPORT OF A CASE TREATED BY PULMONARY RESECTION

Review of the Literature

Jorge A. Taiana, M.D., F.A.C.S.,* Alejandro H. Villegas, M.D.,** and Eduardo Schieppati, M.D.,** Buenos Aires, Argentina

HISTORICAL DATA

In 1933 Kartagener[35] described a syndrome characterized by bronchiectasis, situs inversus totalis, and rhinopharyngosinusopathy. This author accepts as the etiology of the morbid triple association the fact that it is the expression of congenital malformations of varied localization, some at the level of the respiratory tract (lung, rhinopharynx, sinuses) and others at the level of the whole visceral complex (situs inversus totalis).

Actually the first mention of the condition was given by Siewert[62] who, in 1904, reported the case of a 21-year-old man, in whom the three elements of the syndrome were present; this was followed by Oeri's[52] necropsy findings in 1909 and later, in 1923, Guenther's[31] report, where he reports the case of a 19-year-old woman and points out the fact that the patient's sister also presented symptoms of total visceral transposition. Moreover, this author emphasizes the infrequency of situs inversus as its incidence in 63,377 patients registered at Leipzig Institute of Medical Clinics reached only 0.007 per cent.

Although these reports precede Kartagener's chronologically, to this author was left the merit of the interpretation and etiological correlation of the different components of the syndrome, that had undoubtedly escaped the attention of those who believed they were describing a mere morbid casual association. Kartagener explained his theory in successive reports,[35, 36, 37] gathering a total of 11 cases in 1935.

REVIEW AND DISCUSSION

In a careful review of the world literature, we have found 104 cases reported, 8 of which were published by Argentine authors.

The most important series have been reported by Olsen[54] and by Torgensen[63, 64] who have published 14 cases each; Kartagener and Horlacher[35, 36, 37] have reported 11 cases; Adams and Churchill,[14] 5 cases; Lopez Areal,[42] 4 cases; Conway,[26] 4 cases; Neumann,[50] 3 cases; Brügger,[22] 3 cases; Nüssel and Helbach,[51] 2 cases; Jacob, Langle, and Langle,[33] 2 cases; Allende and Langer,[2] 2 cases; Chattas, di Rienzo, and Piantoni,[4] 2 cases; Russakoff and Katz,[59] 2 cases. The reports of isolated cases have been made by: Siewert[62]; Oeri[52]; Guenther[31];

From the Institute of Thoracic Surgery, Buenos Aires, Argentina.
Received for publication Nov. 29, 1954.

*Professor of Thoracic Surgery, University of Buenos Aires. Chief Thoracic Surgeon, Institute of Thoracic Surgery, Buenos Aires.
**Instructor of Thoracic Surgery, University of Buenos Aires. Thoracic Surgeons, Institute of Thoracic Surgery, Buenos Aires.

Berhman[19]; Kautzky[38]; Aguilar, Nijensohn, and Guaglianone[1]; Casaubon and Derqui[3]; Klopstock[40]; Wernli-Haessig[66]; Lilienthal[41]; Flick[28]; Churchill[23]; H. Meyer[44]; F. Meyer[43]; Glaum[30]; Jedlicka and Petrikova[34]; Becker[18]; Rosenthal[58]; Cole and Nalls[25]; Nagy[49]; Murray[48]; Adland and Einstein[15]; Oettli[53]; Richard[57]; Delp[27]; Benda and Huet[20]; Weill, Lallemant, and Leveque[65]; Andrews[17]; Langer[6]; Blixenkrone-Moller[21]; Alves Meira and Ferreira[16]; Fraga Filho, Nery, and Maranhao[29]; Kay and Meyer[39]; Zuckerman and Wurtzebach[67]; Dassen and Gotlieb.[5]

Of the mentioned authors, the cases in which operation was performed were reported by Lilienthal (left lower lobectomy), Flick (right lower lobectomy), Ingraham (lobectomy on both sides), Churchill (middle lobe lobectomy and left lower lobectomy), and Allende and Langer (lobectomy in three cases).

There are arguments both in favor of a common congenital origin of the three elements of the syndrome of Kartagener and in favor of a mixed etiology—congenital and acquired—of bronchiectasis and rhinosinusopathy.

Sayé[61] and Meyer[44] have found bronchiectasis in twins; Pastore and Olsen[55] have discovered bronchiectasis and absence of frontal sinuses in identical twins; Kay and Meyer[39] observed Kartagener's syndrome associated with an anomalous left subclavian artery. Weill, Lallemant, and Leveque[65] described another case, in which the patient's brother presented a congenital malformation of the heart of the "Fallot type." Cockayne,[24] studying the etiopathology of visceral transposition, could prove its presence in members of different families related in various ways. In the cases observed by him, visceral malformation was not associated with bronchiectasis. Kautzky[38] mentioned three cases of situs inversus totalis in which no bronchial dilatation was present. Other authors as Nüssel and Helbach,[51] Behrman,[19] Benda and Huet,[20] and Oettli,[53] who dealt specifically with Kartagener's syndrome, supported a mixed etiology and divided it into congenital predisposition and acquired infection.

In 1937, Adams and Churchill[14] reported 5 cases and analyzed the experience at the Massachusetts General Hospital, where, in a total of 232,112 patients registered, 712 were bronchiectatic and 23 presented visceral transposition; of the latter, 5 had Kartagener's syndrome. The authors pointed out that 21.7 per cent of the patients with situs inversus totalis had bronchiectasis and rhinosinusopathy, while only 0.3 per cent of the total number of patients registered presented these affections.

Olsen[54] analyzed the experience at the Mayo Clinic, where, in 22 years, 85 cases of total visceral transposition have been observed, 14 of which have presented bronchiectasis and rhinosinusopathy. The frequency of bronchiectasis in relation to the total number of patients registered was 0.5 per cent, while in patients with situs inversus, they appeared in 16.5 per cent. Such statistical data made them favor the existence of a congenital factor.

Russakoff and Katz[59] mentioned two cases and made a review of the world bibliography until 1946, finding only 50 cases reported. Without saying anything definite as to etiology, they pointed out the frequency with which patients with situs inversus present bronchiectasis, saying that it is advisable to search for the condition in all cases of visceral inversion.

Lopez Areal[42] made a careful study of the subject reporting four cases. Torgensen[63, 64] found 14 cases of Kartagener's syndrome in 129 visceral transpositions, 123 of which were total and in 8 per cent were accompanied by nasal polyposis. The coincidence of situs inversus and bronchiectasis in several members of a family, is, according to him, an argument in favor of a common congenital origin for both affections. In 1951, Conway[26] reported 4 cases and advocated congenital etiology. In the same year, Zuckerman and Wurtzebach[67] reported another case.

CASE REPORT

G. M. E., 21-year-old male laborer. Admitted Nov. 6, 1953.

Familial and Personal History.—Unimportant.

Present Disease.—Began during early childhood with episodic catarrh of the respiratory tract, after which a permanent mucopurulent bronchorrhea appeared. Periodic impairments during winter. He obtained only temporary relief upon symptomatic treatment. Mucopurulent nasal secretions. He had had no hemoptysis. At the time of hospitalization he had 200 c.c. of mucopurulent expectoration, mainly during the morning and in left lateral decubitus.

Physical Examination.—a, Respiratory tract: moist râles with medium and large bubbles in both lower pulmonary fields, more marked and abundant in the right side where there was also a syndrome of hypoventilation; "sounds" of secretions in trachea and larger bronchi. *b.* Abdomen: hepatic dullness to the left, and tympany of the Traube space to the right. Cecal gurgling in the left iliac fossa and palpation of the ileosigmoid in the right iliac fossa. *c,* Cardiovascular examination: complete dextrocardia with aortic arch to the right, and descending aorta to the left. ECG: see Fig. 1. Rhinolaryngologic examination: intense edema and diffuse congestion of all the pharyngeal and nasal mucosa, the latter with purulent exudates; marked hypertrophy of the lymphatic elements with mucosa of localized polypoid aspect; veiled paranasal sinuses with no signs of acute sinusitis in activity (Fig. 6); external bilateral otitis.

Laboratory Data.—Slight hypochromic anemia (red-cell count, 3.7 million per cubic millimeter). Repeated acid-fast bacilli investigations in sputum: negative. The remaining examinations were normal.

X-Ray Examination.—Fluoroscopy of the thorax: complete inversion of the cardiovascular silhouette; heart apex, pulmonary arch, and aortic notch to the right; remains of Lipiodol in both pulmonary fields, corresponding to previous bronchographies. Gastric bubble to the right; the left hemidiaphragm was two fingerbreadths higher than the right one; normal diaphragmatic movement; hepatic shadow to the left (Fig. 1). (See Figs. 2 to 9, inclusive.)

Bronchoscopy.—Mucopurulent secretions in the basal bronchi where the mucosa was red and swollen.

Functional Exploration of the Lungs.—Ventilatory reserves: 90 per cent, the maximum breathing capacity and the vital capacity corresponded to a 70 per cent and an 85 per cent, respectively, of the theoretical figures. Broncho-

spirometry; the left lung (placed in the right hemithorax) showed a 32 per cent hematosis and a 23 per cent ventilation. Oximetry arterial blood (femoral artery) saturation was 95.8 per cent in rest and exertion.

Diagnosis.—Situs inversus totalis, bilateral bronchiectasis with right predominance, chronic hypertrophic rhinopharyngosinusitis, external otitis.

Preoperative Treatment.—A hygienic dietetic regimen was established; parenteral and aerosol antibiotics, vitamin therapy, hepato-ferrotherapy, postural drainage, exercises, respiratory re-education, and treatment of the rhinopharyngosinusitis by a specialist. This treatment was carried out for 7 months, at the end of which time the clinical situation of the patient was as follows: he had gained 17 kilograms in weight, was in excellent general condition, had a normal red-cell count and blood-volume, and the expectoration had been reduced from 200 c.c. daily to 50 c.c., and the septic foci in upper respiratory tract were controlled. It was decided to undertake the resection of the more affected pulmonary segments (right side, left lung).

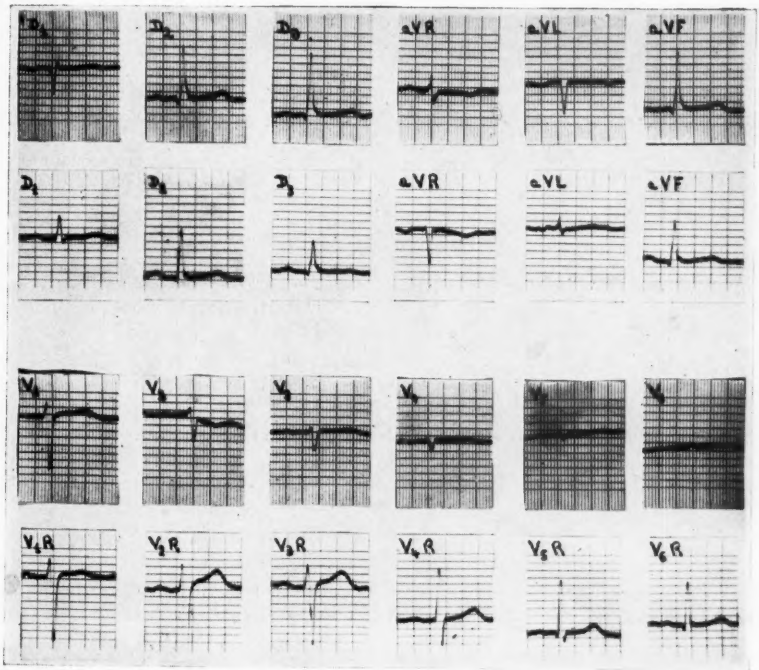


Fig. 1.—The schema corresponding to the superior rows of both groups belongs to an ECG obtained with the classical technique. The one situated in the inferior part of both groups corresponding to an ECG taken with inversion of the cables of the upper limbs, placing points of the precordial single-poles on the right hemithorax. ECG diagnosis: complete dextrocardia with total positional inversion of the cardiac cavities.

Operation.—May 21, 1954: General anesthesia with endotracheal intubations; Pentothal, curare, intravenous Novocain were used. In left lateral decubitus, a right posterolateral thoracotomy was performed with pleurotomy through

Fig. 2.

Fig. 3.

Fig. 4.

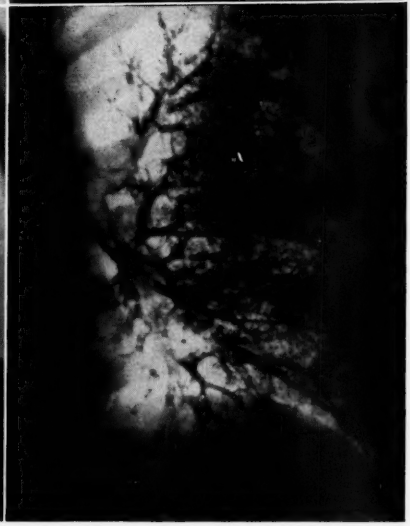


Fig. 5.

Fig. 2.—Confirms what had been observed in fluoroscopy: complete inversion of the cardiovascular silhouette; heart apex, bulge of the pulmonary artery, and aortic notch to the right; remains of Lipiodol in both pulmonary fields; gastric chamber to the right; hepatic shadow to the left; the left hemidiaphragm is two fingerbreadths higher than the right one.

Fig. 3.—(Right bronchography.) Large cylindrical and saccular bronchiectasis of the lower lobe, the lingula, and the anterior segment of the upper lobe. It should be noticed that although it is the right hemithorax, the bronchial pattern corresponds to a left lung. The gastric chamber is shown with an hydroaerial level.

Fig. 4.—(Right bronchography, lateral view.) Confirms what has been observed in the frontal bronchography, showing the involvement of the anterior segment of the upper lobe, of both lingular bronchi, and of the basal bronchi of the inferior lobe.

Fig. 5.—(Left bronchography.) Small cylindrical bronchiectasis of the basal bronchi. It must be noted that although it is the left hemithorax, bronchial pattern is typically right; also, the shadow corresponding to the liver can be observed.

the fifth space; pleura partially adhered. Anatomy corresponded exactly to that of a left hemithorax; two-lobed lung with complete fissure, heart apex, pulmonary artery, aortic arch and thoracic aorta placed in this hemithorax. No major azygos vein. Typical lower lobectomy was first performed; then followed by lingulectomy and anterior segmentectomy of the upper lobe with dissection

Fig. 6. Fig. 7.

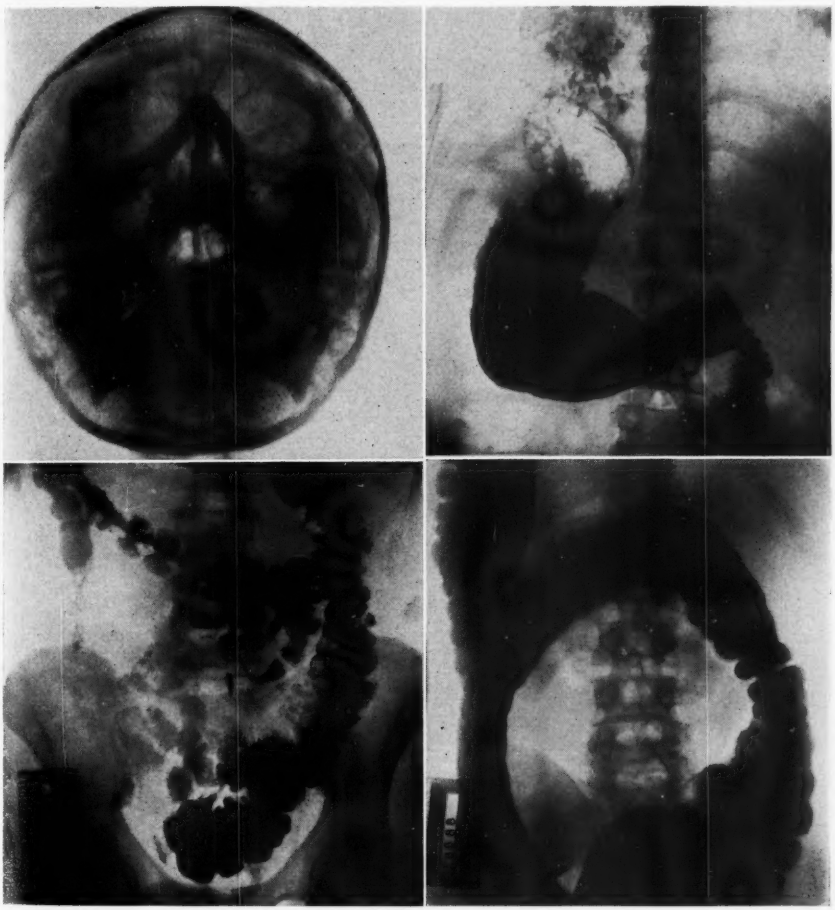


Fig. 8. Fig. 9.

Fig. 6.—Slight diffuse veiling of paranasal sinuses.

Fig. 7.—Completely inverted arrangement of the stomach and the duodenal frame; to the left, the shadow corresponding to the liver.

Fig. 8.—(Twenty-four-hours after barium ingestion.) The filling of the cecum and of the ascending colon in left arrangement is observed; part of the opaque mixture has reached the transverse and the descending colon; rest of barium mixture is in the small bowel. The splenic flexure of the bowel (in this case to the right) adopts a high position while the hepatic flexure (in this case, to the left) is descended and in subhepatic position.

Fig. 9.—(Barium enema.) The complete arrangement of the bowel is observed; raised right flexure (splenic).

and separate ligation of the elements of the segmentary pedicles; blunt dissection of the intersegmentary layer between the anterior and apicoposterior segments of the upper lobe, aided by gentle traction of the corresponding segmentary pedicle. "Block" resection of the lingula and of the anterior segment of the upper lobe. Vascular ligations with silk and closure of the bronchi with interrupted stitches of silk with an Atraumatic needle; in the stump of the lower lobular bronchus, a chromic catgut No. 0 suture was added. Vasculobronchial anatomy corresponded exactly to that of the left lung. Pulmonary re-expansion with hyperpressure, double pleural drainage with apical and basal Nélaton catheters, antibiotics in the pleural cavity; closure of the thoracotomy in the usual way; drainages connected to a water-sealed system with permanent suction.

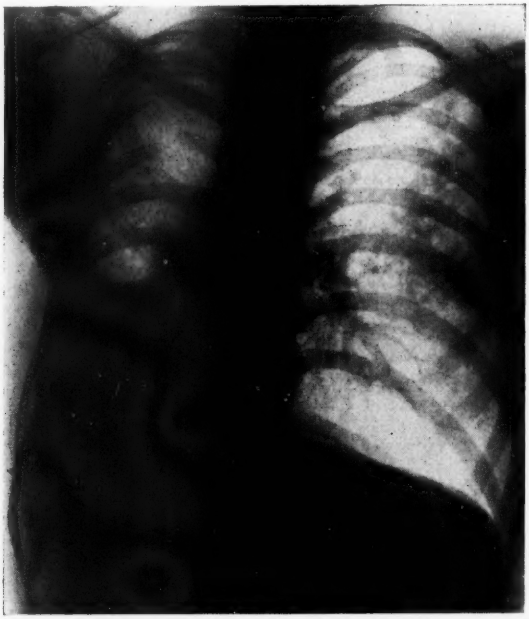


Fig. 10.—(Three-and-one-half months after the operation.) Excellent pulmonary re-expansion and thoracic readjustments; the fifth and sixth interrupted ribs are observed; rise of the right hemidiaphragm and slight pleural sequels.

Postoperative Evolution.—Atelectasia of the remaining parenchyma that was solved by means of bronchosuctions; aseptic serohematic leakage in the operated hemithorax that was drained by repeated punctures followed by instillation of antibiotics. Discharged on Oct. 8, 1954, cured. Conditions at this moment: two or three morning sputa of mucus, he maintains his gain in weight of 17 kilograms; functional exploration of the lungs: ventilatory reserves, 88 per cent, maximum breathing capacity, 48 per cent, and vital capacity, 57 per cent of theoretical figures. The x-ray examination of the thorax showed an excellent thoracic readjustment with full pulmonary re-expansion (Fig. 10).

COMMENTARY AND CONCLUSIONS

We have presented the case of a 21-year-old man with Kartagener's syndrome, whose predominant symptomatology was a mucopurulent bronchorrhea reaching 200 c.c. per day, attributed to large bronchiectases of the left lung (right hemithorax). He was also in very poor general condition. After 7 months of intense preoperative treatment, in which a definite relief was achieved, a right thoracotomy was performed, and was followed by a left lower lobectomy, linguleetomy, and anterior segmentectomy of the upper lobe.

It is interesting to point out that the pathologic anatomy of the surgical specimen was not different from that observed in common bronchiectasis of the "acquired type" (Fig. 11).

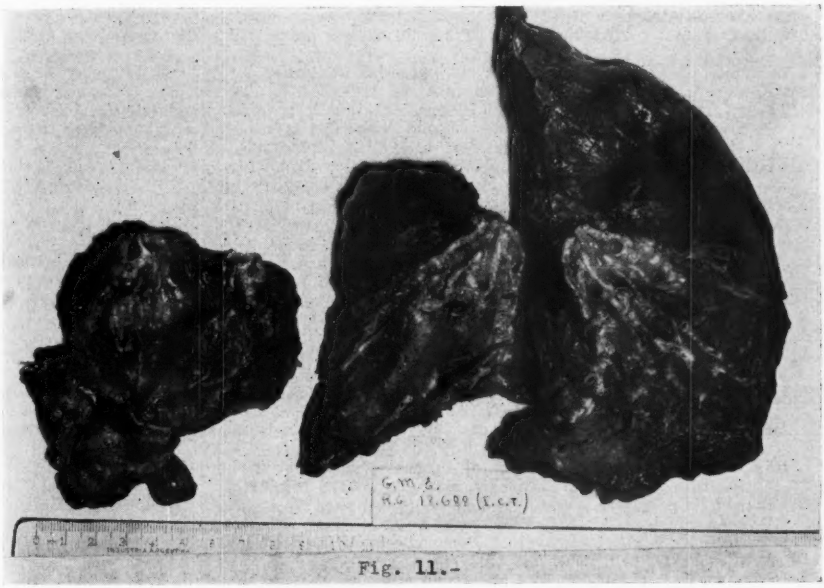


Fig. 11.-

Fig. 11.—(Dr. Fernandez Luna.) Surgical specimens: the lower left lobe (sectioned in two parts) and the lingula and anterior segment of the upper lobe (in a "block") showing large bronchiectasis. Microscopic findings: multiple bronchiectasis with edema of the corium; increase of connective tissue and slight emphysema. The microscopic findings correspond to common bronchiectasis of the "acquired" type.

SUMMARY

Kartagener's syndrome is discussed. The infrequent observation of this syndrome is emphasized and the different theories as to its pathogenesis are analyzed. A review of the world medical literature is given.

A case is reported which has been treated by lower left lobectomy, linguleetomy, and segmentectomy of the anterior segment of the left upper lobe. The patient is cured.

REFERENCES

1. Aguilar, O. P., Nijensohn, A., and Guaglianone, A.: Pulmón en "panal abierto" y "situs inversus totalis." Libro de Oro ofrecido al Dr. Alejandro A. Raimondi, Buenos Aires, 1936, Ed. Aniceto López, p. 250.
2. Allende, J. M., and Langer, L.: Transposición de visceras. Bronquiectasia y sinusitis. Sindrome de Kartagener. Descripción de dos casos, Cirugía **1**: 176, 1947.
3. Casaubon, A., and Derqui, J. C.: Bronquiectasia congénita, Situs inversus, Arch. argent. de pediat. **8**: 471, 1937.
4. Chattas, A., di Rienzo, S., and Piantoni, C.: Bronquiectasia en la infancia. Aspectos clínico-radiológicos, Arch. argent. de pediat. **35**: 278, 1951.
5. Dassen, R., and Gotlieb, D.: Sindrome de Kartagener. A propósito de un caso, Prensa méd. argent. **39**: 249, 1952.
6. Langer, L.: Bronquiectasia en el adulto, Vigésimo Congreso Argentino de Cirugia, Buenos Aires, 1949, Ed. Tall. Gráf. de la Prensa Médica, p. 1.
7. Villegas, A. H.: Bronquiectasias bilaterales, Tesis de Doctorado, Biblioteca de la Facultad de Ciencias Médicas, Buenos Aires, 1952.
8. Taiana, J. A.: A propósito de bronquiectasias, Clín. Tórax, Bs. As. **1**: 277, 1949.
9. Taiana, J. A.: Bronquiectasias bilaterales. Primer congreso Argentino de Cirugía Torácica. Quintas Jornadas Argentinas de Cirugía Tofácica, Buenos Aires, 1953, Ed. El Ateneo.
10. Taiana, J. A.: Bronquiectasias. Tratamiento quirúrgico, Clín. Tórax, Bs. As. **4**: 12, 1952.
11. Taiana, J. A., and Schieppati, E.: Lobectomías bilaterales. Segundas Jornadas Argentinas de Cirugía Torácica, Buenos Aires, 1949, Ed. El Ateneo.
12. Taiana, J. A., Schieppati, E., and Villegas, A. H.: Bronquiectasias bilaterales. Comentario sobre 16 casos operados, Comunicado al Congreso Internacional de Cirugía, Madrid, mayo de 1952, Idem. Anales de Cirugía. **11**: 163, 1952.
13. Taiana, J. A., Schieppati, E., and Villegas, A. H.: Bronquiectasias bilaterales. Tratamiento médico y quirúrgico en 52 casos, Clín. Tórax, Bs. As. **5**: 5, 1953, Rev. Asoc. med. argent. **68**: 57, 1954.
14. Adams, R., and Churchill, E. D.: Situs Inversus, Sinusitis, Bronchiectasis. A Report of Five Cases, Including Frequency Statistics, J. THORACIC SURG. **7**: 206, 1937.
15. Adland, S. A., and Einstein, R. A. J.: Kartagener's Triad; Situs Inversus Viscerum, Bronchiectasis and Paranasal Sinusitis, A. M. A., Am. J. Dis. Child. **61**: 1034, 1941.
16. Alves Meira, J., and Ferreira, M.: Tríade de Kartagener, em paciente com Equistosomose Mansoni e moléstia de Chagas, Rev. med. e cir. São Paulo **10**: 9, 1950.
17. Andrews, C. T.: Kartagener syndrome, Brit. M. J. **2**: 1269, 1949.
18. Becker, B.: Über einen Fall von angeborenen Bronchiektasen bei Situs viscerum inversus totalis, Beitr. Klin. Tuberk. **94**: 73, 1939.
19. Behrman, A.: Über die Symptomentrias Situs inversus, Bronchiektasien und Polyposis nasi, Beitr. Klin. Tuberk. **86**: 161, 1935.
20. Benda, R., and et Huet, P.: Un cas de syndrome de Kartagener chez un enfant de sept ans, Bull. mém. Soc. méd. hôp. Paris **64**: 252, 1948.
21. Blixenkrone-Moller, N.: Congenital bronchiectasis, allergic lung infiltration and situs inversus organorum, Acta chir. scandinav. **100**: 161, 1950.
22. Brügger, H.: Nichttuberkulöse Höhlenbildungen im Thoraxraum bei Kindern, Monatsschr. Kinderh. **77**: 372, 1939.
23. Churchill, E. D.: Lobectomy and Pneumonectomy in Bronchiectasis and Cystic Disease, J. THORACIC SURG. **6**: 286, 1937.
24. Cockayne, E. A.: The Genetics of Transposition of Viscera, Quart. J. Med. **27**: 439, 1938.
25. Cole, D. B., and Nalls, W. F.: Situs Inversus, Sinusitis, and Bronchiectasis, J. THORACIC SURG. **9**: 689, 1940.
26. Conway, D. J.: A Congenital Factor in Bronchiectasis, Arch. Dis. Childhood. **26**: 253, 1951.
27. Delp, M. H.: Kartagener's triad. Situs inversus, Absent Frontal Sinuses With Maxillary Ethmoid and Sphenoid Infection, and Bronchiectasis, J. Kansas M. Soc. **47**: 93, 1946. Quoted by Russakoff, A. H. and Katz, H. W.[59]
28. Flick, J. B.: Discussion on the paper of Adams, R., and Churchill, E. D.[14]
29. Fraga Filho, C., Boavista Nery, A. L. B., and Maranhao, I.: Tríade de Kartagener, Hospital, Rio de Janeiro **40**: 491, 1951.
30. Glaum, K.: Bronchiektasien bei Situs viscerum inversus totalis, Beitr. Klin. Tuberk. **91**: 422, 1938.
31. Guenther, H.: Biol. Zentralbl. **43**: 175, 1923. Quoted by Kartagener.[35]
32. Ingraham, R.: Case of Situs Inversus With Extensive Bilateral Bronchiectasis Dating From Early Childhood and With Bilateral Lobectomies, M. Women's J. **46**: 593, 1939. Quoted by Olsen, A. M.[54]
33. Jacob, P., Langle, G., and Langle, L.: Bronchiectasie et ethmoidoanthrite. Deux cas nouveaux de syndrome de Kartagener, Bull. et mém. Soc. méd. hôp. Paris **62**: 420, 1946.

34. Jedlicka, and Petrikova: Ref. Ztschr. Tuberk. **82**: 257, 1939, Quoted by Lopez Areal, L.[42]
35. Kartagener, M.: Zur Pathogenese der Bronchiektasien. I. Mitteilung: Bronchiektasien bei Situs viscerum inversus, Beitr. Klin. Tuberk. **83**: 489, 1933.
36. Kartagener, M., and Horlacher, A.: Zur pathogenese der Bronchiektasien; situs viscerum inversus und Polyposis nasi in einem Falle familiärer Bronchiektasien, Beitr. Klin. Tuberk. **87**: 331, 1935.
37. Kartagener, M., and Horlacher, A.: Bronchiektasien bei Situs viscerum inversus, Schweiz. med. Wchnschr. **65**: 782, 1935.
38. Kautzky, A.: Neuere bronchographische Ergebnisse bei Ektasien der Bronchien, Fortschr. Geb. Röentgenstrahlen **54**: 219, 345, 1936.
39. Kay, J., and Meyer, R. N.: Kartagener's Syndrome With an Anomalous Left Subclavian Artery, Brit. J. Radiol. **24**: 27, 1951.
40. Klopstock, R.: Zentralbl. Tuberk. **45**: 392, 1937. Quoted by Lopez Areal, L.[42]
41. Lilienthal, H.: Discussion on the Paper of: Adams, R., and Churchill, E. D.[14]
42. Lopez, Areal, L.: Observación familiar de inversión visceral total con bronquiectasias y pulmón quístico, congénitos, Rev. clín. españ. **14**: 378, 1944.
43. Meyer, F.: Bronchiektasie und das Syndrom Kartageners, Deutsche Militàrarzt. **8**: 197, 1943. Quoted by Russakoff, A. H., and Katz, H. W.[59]
44. Meyer, H. E.: Ueber Bronchiektasien bei eineiigen Zwillingen, Zentralbl. f. inn. Med. **59**: 255, 1938.
45. Meyer, H. E.: Bronchiektasien und Erbanlage, Beit. Klin. Tuberk. **94**: 264, 1940. Commented by Lopez Areal, L.[42]
46. Meyer, H. E., und Rolfs, O. H.: Ergebnisse bronchographisher Untersuchungen, Beit. Klin. Tuberk. **92**: 1, 1938.
47. Mounier-Kuhn, P.: Le syndrome "ethmoïdo-antrite et bronchiectasies." Clinique. Etiologie. Hypothèses pathogeniques, Ann. oto-laryng. 1-2-3: 387, 1944.
48. Murray, G. M.: Kartagener's Syndrome, Canad. M. A. J. **64**: 248, 1951.
49. Nagy, L.: Über congenitale Bronchiektasen an Hand, eines Falles von Situs viscerum inversus totalis, Beitr. Klin. Tuberk. **95**: 26, 1940.
50. Neumann, W.: Klinische Beobachtungen zur Aetiologie der chronischen Bronchiektasien, Med. Klin. **34**: 738, 1944.
51. Nüssel, K., and Helbach, A.: Bronchiektasien bei Situs viscerum inversus totalis (zugleich ein Beitrag zur Pathogenese der Bronchiektasien, Beitr. Klin. Tuberk. **84**: 424, 1934.
52. Oeri, R.: Frankfurt. Ztschr. f. Path. **3**: 393, 1909. Quoted by Kartagener, M.[35]
53. Oettli, O.: Beitr. Klin. Tuberk. **97**: 655, 1942. Quoted by Lopez Areal, L.[42]
54. Olsen, A. M.: Bronchiectasis and Dextrocardia. Observations on the Aetiology of Bronchiectasis, Am. Rev. Tuberc. **47**: 435, 1943.
55. Pastore, P. N., and Olsen, A. M.: Absence of Frontal Sinuses and Bronchiectasis in Identical Twins, Proc. Staff. Meet., Mayo Clin. **16**: 593, 1941.
56. Reitter, G. S.: Congenital Bronchiectasis in Children, Radiology **25**: 495, 1935.
57. Richard, W. F.: Situs Inversus Viscerum, Absent Frontal Sinuses With Ethmoid and Maxillary Infection, and Bronchiectasis. Kartagener's Triad. Report of a Case, Tubercle. **25**: 27, 1944.
58. Rosenthal, D. B.: Bronchiectasis and Visceral Transposition With Report of a Case, M. J. Australia **1**: 761, 1939.
59. Russakoff, A. H., and Katz, H. W.: Dextrocardia and Bronchiectasis; Review of Literature and a Report of Two Cases, New England J. Med. **235**: 253, 1946.
60. Sauerbruch, F.: Die Bronchiektasen, Troisiéme Congrés de la Société Internationale de Chirurgie, Bruxelles, 1911.
61. Sayé, L.: Bronquiectasia congénita en dos hermanas gemelos, An. de med. int. **1**: 13, 1932.
62. Siewert, A. K.: Ueber einen Fall von Bronchiectasie bei einem Patienten mit Situs inversus viscerum, Berl. klin. Wchnschr. **6**: 139, 1904. Quoted by Kartagener, M.[35]
63. Torgersen, J.: Familiar Transposition of Viscera, With Preliminary Remarks on Genetics and Correlation With Diseases of Respiratory Tract, Acta med. scandinav. **126**: 319, 1946.
64. Torgersen, J.: Transposition of Viscera. Bronchiectasis and Nasal Polyps. A Genetical Analysis and a Contribution to the Problem of Constitution, Acta radiol. **28**: 17, 1947.
65. Weill, J., Lallemant, M., and Leveque, B.: Un cas de syndrome de Kartagener, Bull. et. mém. Soc. méd. hôp. Paris. 71, 1948.
66. Wernli-Haessig, A.: Situs inversus und Bronchiektasien, Ztschr. Tuberk. **77**: 120, 1937.
67. Zuckerman, H. S., and Wurtzebach, L. R.: Kartagener's Triad. Review of the Literature and Report of a Case, Dis. Chest **19**: 92, 1951.

CONCURRENT PRIMARY LEIOMYOSARCOMA AND CARCINOMA OF THE BRONCHUS

DENNIS ROSENBERG, M.B., CH.B., EDGAR MEDLAR, M.D., AND
RICHMOND DOUGLASS, M.D.
ITHACA, N. Y.

INTRODUCTION

PRIMARY pulmonary sarcomas are rare tumors arising from lymphoid, fibrous, neurogenic, or muscular tissue components of the pulmonary architecture. Reports of primary bronchogenic leiomyosarcoma are extremely uncommon. In a review of the literature in 1946 Randall and Blades[1] were able to collect only 6 cases, and added one of their own. In 1951 Freireich and associates[2] reported one case and, more recently, Johnson and co-authors[3] recorded their experience with a primary pulmonary leiomyosarcoma treated successfully by pneumonectomy, bringing the total number of reported cases to nine.

The concurrence of two tumors in the bronchus, each representing a separate primary neoplasm arising from different germ layers, is even rarer. Ovens and Russell[4] reported a case of concurrent leiomyosarcoma and squamous-cell carcinoma in the esophagus, but we have been unable to find any report in the English literature of such tumors occurring together in the bronchus. For this reason, the following case of a primary leiomyosarcoma and of a primary undifferentiated carcinoma arising concurrently in the bronchus is reported. Of further interest is its successful treatment by pneumonectomy.

REPORT OF CASE

A 62-year-old white man was admitted on Jan. 21, 1953, complaining of fatigue and frequent episodes of pneumonia during the previous fall and winter. Symptoms began during the summer when his chronic cough became more troublesome and more productive of sputum. At this time he also began to experience slight dyspnea. He was treated by his local physician with repeated injections of penicillin. Two weeks before admission he was hospitalized elsewhere for pneumonia, but, because acid-fast bacilli were found in the sputum, transfer to Biggs Memorial Hospital was arranged. There had been a loss of 7 pounds during the month before admission, and night sweats and fever had been noted.

Physical Examination.—Examination of the chest revealed dullness in the right upper third with increased breath sounds and many rhonchi. The left lung was clear on percussion and auscultation.

Laboratory Studies.—Fluoroscopy showed infiltration in the right upper pulmonary field, normal excursion of both diaphragms and no mediastinal shift. Roentgenography (Fig. 1), revealed a dense lesion at the right hilum extending into the pulmonary field, with scattered pneumonic infiltrate throughout the upper third of the right pulmonary field.

The total white blood cell count was 12,350 per cubic millimeter with the differential being neutrophils 60 per cent, lymphocytes 16 per cent, monocytes 9 per cent, eosinophils 14

From the Thoracic Surgical Service, Hermann M. Biggs Memorial Hospital.
Received for publication Dec. 2, 1954.

per cent, and basophils 1 per cent. Sedimentation rate was 67 mm. in one hour (Westergren method). Repeated examinations of the sputum revealed no acid-fast bacilli, neoplastic cells, or fungi. However, a variety of secondary organisms were cultured from the sputum.

Fig. 1.

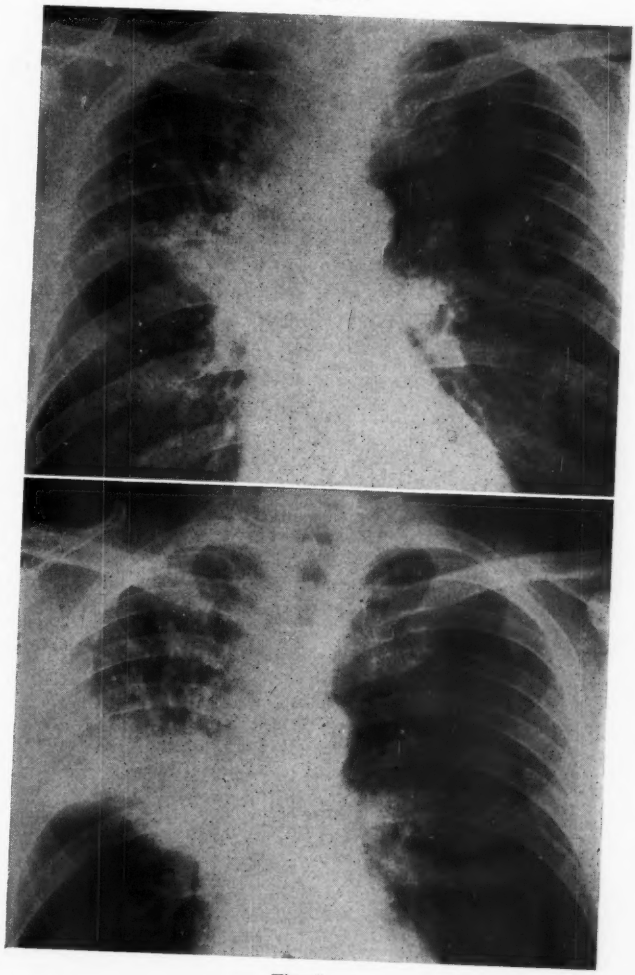


Fig. 2.

Fig. 1.—Chest roentgenogram taken on admission to the hospital.

Fig. 2.—Chest roentgenogram taken one week later. The pulmonary shadows are related to an extensive lobular pneumonia, principally in the upper lobe. None of the shadows are related directly to the tumor of the bronchus.

Course in Hospital.—On the sixth hospital day the temperature rose to 103° F. and the roentgenogram (Fig. 2), showed an increase in the pneumonic process in the right upper pulmonary field. Penicillin and Gantrisin therapy during the next two days resulted in considerable clinical improvement. Bronchoscopy on the tenth hospital day disclosed a cone-shaped mass 2 cm. below the carina projecting into and partially obstructing the right main

bronchus. It appeared to originate near the orifice of the right upper lobe bronchus, which could not be clearly visualized. The trachea and left bronchial tree were considered normal. A biopsy specimen was obtained without excessive bleeding. On microscopic examination it was covered with pseudostratified epithelium, with connective tissue and smooth muscle between the layers of epithelium; mitotic figures were absent and no penetration of epithelium beyond the basement membrane was found. No definite diagnosis of neoplasm could be made.

On the twentieth and twenty-first hospital days, two attacks of paroxysmal dyspnea occurred, with complete absence of breath sounds over the entire right lung. During a violent episode of coughing the patient raised a piece of tissue which measured 1 by 1 by 0.5 cm. Microscopic examination of this disclosed no recognizable cells since the tissue was all necrotic.

Bronchoscopy on the twenty-first hospital day again showed an irregular mass in the right main-stem bronchus. A considerable amount of secretion was aspirated from below the mass, and a biopsy was again done for microscopic examination. The pathologic report on this third specimen was that again only necrotic tissue was present. The process was suggestive of neoplasm, the nature of which could not be determined.

Operation.—On the twenty-seventh hospital day, at exploratory thoracotomy, palpation revealed a rounded mass within the right main-stem bronchus which could be displaced sufficiently to permit safe clamping of this bronchus proximally. Pneumonectomy was completed without untoward incident.

Postoperative Course.—Apart from some difficulty in expectorating secretions and occasional episodes of slight dyspnea, the patient had an uneventful postoperative convalescence and was discharged March 27, 1953. Since then, frequent examinations in the outpatient department, the most recent on July 10, 1954, reveal that he feels well, is not dyspneic, has gained weight, and has resumed his usual work.

Macroscopic Examination.—Shortly beyond the resected bronchus a reddish-gray mass protruded from the upper lobe bronchus into the main-stem bronchus, the free projecting portion measuring 2 by 2 by 1 cm., and in this position indicating a potent ball-valve mechanism. Lymph nodes in the hilar region were of normal size and consistency. Sections through the upper lobe showed bronchi distended with yellowish purulent material and numerous areas of lobular pneumonia. No abscesses were seen and a considerable portion of the upper lobe was not involved in the pneumonic process. The polypoid mass, which arose from the wall of the upper lobe bronchus (Fig. 3) about 1 cm. from its origin, was mushroom-shaped, the stem being 1.5 by 0.8 cm. The remainder of the upper lobe bronchus appeared normal. The middle and lower lobe lung tissue presented a normal appearance.

Fig. 3.—This is a longitudinal section of the tumor mass. Note the origin of the tumor from the bronchial wall in the lower portion of the illustration; the bronchial wall of the upper lobe bronchus on either side of the tumor up to about the middle of the picture; and the reddish necrotic tip of the tumor in the upper end. It was from this portion of the tumor that microscopic sections showed only necrotic tissue, making preoperative diagnosis impossible. The upper third of the tumor lay in the main-stem bronchus and was visualized on bronchoscopy. (×2.)

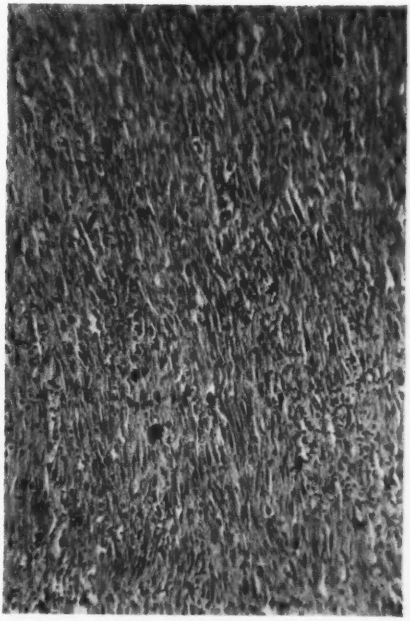
Fig. 4.—This illustration shows the long spindle-shaped cells that characterized most of the tissue as a leiomyosarcoma. Mitotic figures were fairly easily found in these cells. The numerous small blue dots are lymphocytes. The tumor throughout showed an infiltration of leukocytes that in most areas were lymphocytes. However, in some areas, particularly toward the necrotic tip, there was a considerable infiltration of neutrophils. Neutrophils were particularly abundant in the demarcation zone between viable and necrotic tumor tissue (×100.)

Fig 5.—Another field of the tumor showing a marked anaplasia of the tumor tissue with the presence of numerous giant cells. This anaplasia is seen quite often in leiomyosarcomas. (×100.)

Fig. 6.—Illustration of a carcinoma "in situ" of the upper lobe bronchus. Note the normal ciliated columnar epithelium in the upper third of the illustration and the alteration in the character of the epithelium below this normal area. The change in the character of the epithelium occurs rather abruptly. Mitotic figures were easily found in the altered epithelium. In some places, in areas not in the illustration, there was a downgrowth of the epithelium into the submucosa and into mucous glands. This carcinoma in situ was in the upper lobe bronchus and it was directly associated with the leiomyosarcoma. No evidence of tumor metastasis was found in several hilar lymph nodes. Note the similarity of the bands of normal smooth muscle, present in the upper right-hand corner, to the spindle-shaped tumor cells in Fig. 4. (×100.)

Fig. 3.

Fig. 4.



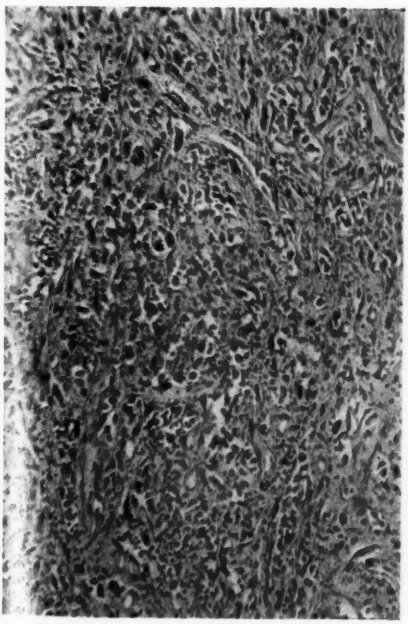


Fig. 5.

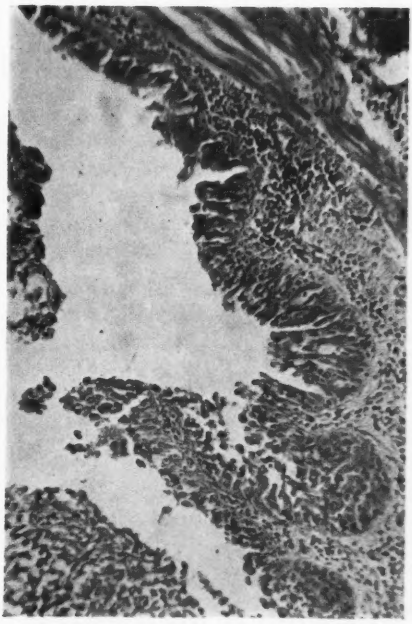


Fig. 6.

Figs. 3-6. *(For legends see opposite page.)*

Microscopic Examination.—Sections through the upper lobe showed numerous areas of lobular pneumonia, organized, organizing, and in a process of resolution. A tumor arising from the wall of the upper lobe bronchus showed only local invasion of the wall. It was composed of long spindle-shaped cells with smooth muscle cell characteristics (Fig. 4). In some portions the tumor tissue was anaplastic with numerous tumor giant cells (Fig. 5) being present. Mitotic figures were readily found in all portions of the tumor tissue and lymphocytic infiltration was present throughout. The distal end of the tumor showed considerable necrosis and neutrophilic infiltration. There was no evidence of metastasis in the hilar lymph nodes. Sections from the lower and middle lobes were normal apart from a few small foci of lobular pneumonia.

Of particular interest was the character of the bronchial epithelium lying adjacent to but separate from the base of the leiomyosarcoma. Here it was possible to demonstrate (Fig. 6) a sudden change from a normal columnar ciliated epithelial lining to a multilayered ovoid to cuboidal epithelium without any ciliated columnar cells. In the area of altered epithelium, mitotic figures were readily found. In some areas the epithelium had grown down into the submucosa and into mucus glands. No evidence was found of tumor tissue in lymph channels or in adjacent hilar lymph nodes. No evidence was found of the carcinomatous change in the bronchial epithelium in the tissue section illustrated in Fig. 3. The carcinoma "in situ" was found because several large blocks of tissue through the hilar portion of the lung were processed for microscopic study. No evidence of carcinomatous change was found in several other sections of other bronchial branches of all lobes, both in the hilar region and out in the lung tissue.

COMMENT

In the examination of numerous blocks of the excised lung an early undifferentiated carcinoma of the bronchus was found to occur independent of the sarcoma. Strikingly different histologic patterns leave no doubt as to the fact that each represents a separate primary neoplasm. The diagnosis of bronchial sarcoma has been successfully made by bronchoscopy on a few occasions, but it must be emphasized that necrosis and hemorrhage are characteristic of this intrabronchial group, and that a true cellular pattern is difficult to obtain. The necrosis of the distal portions of the tumor can be explained by the fact that the neoplasm had outgrown its source of nourishment, as occurs not infrequently in leiomyosarcomas of the uterus. It is not surprising, therefore, that bronchoscopic biopsy of tumors of this nature is of little diagnostic value. From a pathologic view the cytostructural variations found in this type of tumor have always led to confusion. In sections taken from different portions of the same growth many varied histologic appearances may be seen. Whorling of the cells may be prominent in some regions and pseudorosette formations sometimes are present in other areas. The nuclei may vary considerably in size and shape. Mitotic figures may be numerous and tumor giant cells may be a dominant feature in some areas. Apparently the variegated microscopic appearance of these tumors reflects anaplastic tendencies of the tumor growth.

Local removal of the tumor and fulguration of the base, as advocated by Pollak and co-workers,[5] among others, cannot be considered the rational form of therapy. The only logical treatment is pulmonary resection, as in all pulmonary malignant tumors. In the management of these patients Churchill and associates[6] have emphasized the importance of clearing the bronchus by local bronchoscopic removal preoperatively. This makes the lung more

manageable at operation and will help to obviate uncontrollable hemorrhage from the tumor during resection.[1, 7] In the absence of local and distant metastases, resection offers a better prognosis in these tumors than in bronchial carcinoma. Slow growth and late metastases are characteristics of leiomyosarcoma, the tumor often reaching large size yet remaining operable. The prognosis in the case herein reported must, however, be more guarded because of the presence of the early carcinoma.

The clinical and pathologic features illustrated by this case emphasize, too, the picture so often produced by an obstructing lesion of a bronchus, namely, repeated episodes of pneumonitis, temporarily subsiding following administration of antibiotics, but with progressive and eventually irreversible changes in the lung tissue. These changes may be patchy but extensive, sometimes progressing to formation of a frank abscess and frequently obscuring the more important etiologic factor, the obstructing tumor.

SUMMARY

A case of primary leiomyosarcoma of the bronchus, which is believed to be the tenth such report in the English literature, is presented. This case is even more unusual because of the presence of an independent concurrent early primary bronchogenic carcinoma. This is believed to be the first such combination occurring in the lung to be reported in the English literature. Currently the patient is asymptomatic and back to full-time work some twenty months following discharge.

REFERENCES

1. Randall, W. S., and Blades, B.: Primary Bronchiogenic Leiomyosarcoma, Arch. Path. **42**: 543-548, 1946.
2. Freireich, K., Bloomberg, A., and Langs, E. W.: Primary Bronchogenic Leiomyoma, Dis. Chest. **19**: 354-358, 1951.
3. Johnson, E. K., Mangiardi, J. L., and Jacobs, J. B.: Primary Leiomyosarcoma of the Lung Treated by Pneumonectomy, Surgery **32**: 1010-1013, 1952.
4. Ovens, J. M., and Russell, W. O.: Concurrent Leiomyosarcoma and Squamous Carcinoma of the Esophagus, A. M. A. Arch. Path. **51**: 560-564, 1951.
5. Pollak, B. S., Cohen, S., Borrone, M. G., and Gnassi, A. M.: Primary Sarcoma of the Bronchus; Case Report, Am. J. Roentgenol. **41**: 909-914, 1939.
6. Churchill, E. D., Sweet, R. H., Soutter, L., and Scannell, J. G.: Surgical Management of Carcinoma of the Lung; Study of Cases Treated at Massachusetts General Hospital From 1930 to 1950, J. THORACIC SURG. **20**: 349-358, 1950.
7. Massachusetts General Hospital Case 33322: Bronchial Adenoma of Right Main Bronchus, With Hemorrhage Into Left Lung, New England J. Med. **237**: 198-201, 1947.

PNEUMONECTOMY AND PULMONARY VALVULOTOMY IN THE TREATMENT OF ACTIVE TUBERCULOSIS AND PULMONARY STENOSIS

Report of a Case

Lamar Soutter, M.D.,* J. Gordon Scannell, M.D.,** and Gordon S. Myers, M.D.***
Boston, Mass.

ONE of the most stimulating advances in modern medicine during the last decade has been the development of cardiac surgery, particularly in operations on the heart valves. Although the approach at first was indirect, as experience and knowledge of cardiac anomalies and physiology advanced, the attack became increasingly direct. No problem illustrates this better than that of pulmonary stenosis. When Blalock and Taussig[1] first created an artificial shunt to increase the pulmonary blood flow in tetralogy of Fallot, the first step was taken. Within four years, both Brock[2] and Sellors[3] had successfully carried out pulmonary valvulotomy by insertion of a valvulotome through the right ventricle. The simplicity, low mortality, and success of this procedure led to its widespread acceptance in the treatment of pure pulmonary valvular stenosis. Recently, Dodril,[4] using an artificial by-pass of the right side of the heart, and Swan and associates,[5] employing hypothermia, have successfully opened the pulmonary artery and operated on the valve under direct vision.

The extraordinary achievements of Blalock and Brock created a demand for accurate diagnosis of cardiac anomalies. Both cardiac catheterization and angiocardiographic examination, as well as other studies, have become important diagnostic tools in establishing preoperatively the exact nature of cardiovascular defects. Unfortunately, pulmonary stenosis is variable in type and often complicated by other anomalies that militate against complete cure by valvulotomy.

Some of the variations in type introduce serious technical problems; some of the associated anomalies may vitiate seriously the results achieved by valvulotomy. Forms of obstruction to blood flow from the right ventricle to the pulmonary vessels include stenosis of the valve cusps, thickening of the myocardium narrowing the outflow tract of the right ventricle, membranous

From the Massachusetts General Hospital, Boston, Mass.

This study was supported in part by a research grant from the National Heart Institute of the United States Public Health Service.

Received for publication Jan. 24, 1955.

*Clinical Associate in Surgery, Massachusetts General Hospital; Associate Professor of Surgery, Boston University.

**Assistant Surgeon, Massachusetts General Hospital; Clinical Associate in Surgery, Harvard Medical School.

***Assistant Physician, Massachusetts General Hospital; Associate in Medicine, Harvard Medical School.

obstruction in the ventricle proximal to the valve, and atresia of the pulmonary artery. The term infundibular stenosis has been applied both to the muscular and membranous forms of obstruction. Although these variations usually exist separately, they may be found in combination. All have been treated surgically by incision and dilatation, and occasionally by excision when suitable. Stenosis of the valve itself is the most amenable to surgery; pulmonary atresia the least, although Glover and associates[6] have reported initial success using dilatation in 3 cases.

The commonly associated anomalies are interatrial or interventricular septal defects, with or without dextroposition of the aorta. In general, the presence of these associated anomalies seldom constitutes a contraindication to operations for improving the pulmonary arterial flow. In many instances, although the circulation is not restored to normal by such procedures, the improvement in the patient's general condition is dramatic.

The pathological anatomy of the stenosed valve is of great importance because it has strongly influenced the surgical approach to correct it. As a rule, the cusps are fused into a thin membrane, which, by force of inreased intraventricular pressure balloons out into the artery. The attack with a valvulotome is relatively simple through a ventricular incision because it can readily be passed into the taut, cup-shaped valve. At the same time, infundibular stenosis, if present, is more amenable to lysis, stretching, or excision by this approach. In some cases of long-standing stenosis, the valve may become thickened, vegetations may grow on it, or it may become calcified.

In pure valvular stenosis, excision under direct vision through the open artery offers a better opportunity for the establishment of a large opening, as Swan and co-workers[5] have so readily demonstrated. Right ventricular pressures may be restored to completely normal levels by this process. The element of regurgitation introduced by the production of a large opening in the valve has not as yet been assessed for its harmful effects. Whether a large opening is actually necessary is another question. Litwak and associates[7] have stated that embarrassment of cardiac function does not occur until the occlusion of the outlet is greater than 75 per cent. Although we do not know yet just how large an opening is necessary, cases showing persistence of right ventricular pressures considerably above normal postoperatively may, nevertheless, show gratifying clinical improvement.[8, 9] The point made by Deterling[10] that the pressure should be ascertained by direct catheterization immediately after valvulotomy seems a reasonable one, as it offers a fairly reliable check on what has been accomplished at a time when the valvulotome may be easily reinserted.

The fate of the untreated case of pulmonary stenosis is of great interest to the clinician in the planning of surgery. Greene and associates,[11] in reporting their own cases and reviewing the literature, found the average length of life in 62 patients to be twenty-six years. Causes of death were recorded for 59 patients: 27 died of heart failure, 10 of tuberculosis, 7 of vegetative endocarditis, and 15 of various other diseases. The life span is more abbreviated in tetralogy of Fallot and in other cases in which pulmonary stenosis accompanied

septal defects. In most series, the mortality has been preponderantly due to heart failure, anoxia, or bacterial endocarditis.[12, 13] The incidence of tuberculosis is variable. Hawes[14] cited Norris as saying that one-third of 449 patients with pulmonary stenosis who were examined at autopsy also had tuberculosis. In most of the recent series, however, it is far less common than this, particularly in those reported by surgeons. Sellors'[3] case is a notable exception. White,[15] in discussing the combination of tuberculosis and valvular heart disease, remarked that the pulmonary circulation is engorged in mitral stenosis, in which tuberculosis is quite rare, but may be deficient in pulmonary stenosis, in which tuberculosis is quite common.

The relation of diabetes and tuberculosis has been reported by a number of investigators. Reaud[16] found an incidence of 0.98 per cent in 3,850 tuberculous patients. Ferrara[17] found that 2.1 per cent of 3,178 tuberculous patients had diabetes. Both authors indicated that the pulmonary disease was likely to be more advanced among diabetic than nondiabetic patients and, therefore, the prognosis was more grave. The diabetic patients, however, did as well as other patients with similar degrees of infection once therapy had been instituted.

We present the following case in which the coexistence of advanced pulmonary tuberculosis and pulmonary stenosis posed a difficult problem in judgment and dictated an unusual surgical approach.

CASE REPORT

L. O. (M.G.H. 829049), a 30-year-old man, was admitted to the hospital. When he was 6 years of age a systolic murmur had been noted, but it had not interfered with normal development and he had been able to participate in all sports throughout the school years. When he was 23 years of age, he started to lose weight and did not feel well. Examination disclosed the presence of diabetes, which required 40 units of protamine zinc insulin daily. Despite a diet and insulin, he continued to lose weight, and developed a productive cough. A roentgenogram of the chest (Fig. 1) disclosed multiple densities in the left lung and a cavity in the left upper lobe. The right lung was clear. The sputum contained tubercle bacilli, and the patient was sent to a sanitarium. On bed rest and streptomycin the right lung remained clear, but a sizable cavity persisted in the left hemithorax, and the sputum remained positive. The patient became increasingly dyspneic and cyanotic, and there was clubbing of the fingers. At this time, a diagnosis of pulmonary stenosis was made. Resection of the left lung was considered, but rejected as being too hazardous. Therefore, a cavernostomy (Monaldi procedure) was carried out through the second interspace anteriorly. A year later, although there was persistent drainage from the cavity requiring a tube, the patient returned to his home. The cavity was reduced in size but the sputum and drainage remained positive. The patient gained some weight but was confined to a bed-and-chair existence. After two years he was no better and the question of surgery was again raised.

When admitted to our hospital the patient was thin, cyanotic, and dyspneic on the slightest exertion. The temperature, pulse, and respirations were normal at rest. A harsh systolic murmur was heard in the pulmonic area. The left side of the chest was dull to percussion, and purulent fluid was still draining through a small anterior catheter. The fluid was positive for tuberculosis on smear. The sputum was small in amount, and positive on culture. The white-cell count was 11,700, the hemoglobin 19.3 Gm. per 100 c.c., and the hematocrit 54 per cent. Other laboratory studies were negative. The diabetes was well controlled on 40 units of insulin.

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

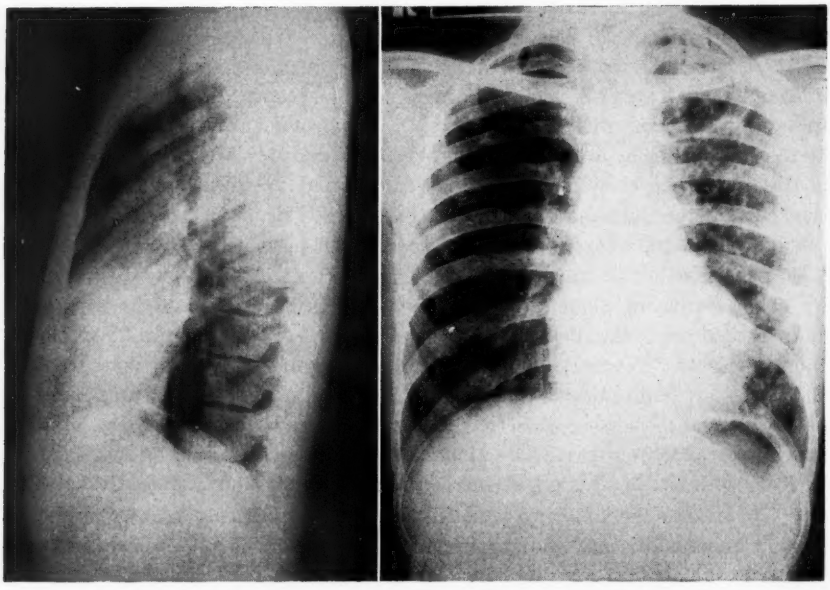


Fig. 1.—Roentgenograms of the chest when pulmonary tuberculosis was first diagnosed. There is a diffuse infiltration of the left lung and a cavity in the upper lobe. The cardiac contour is not remarkable.

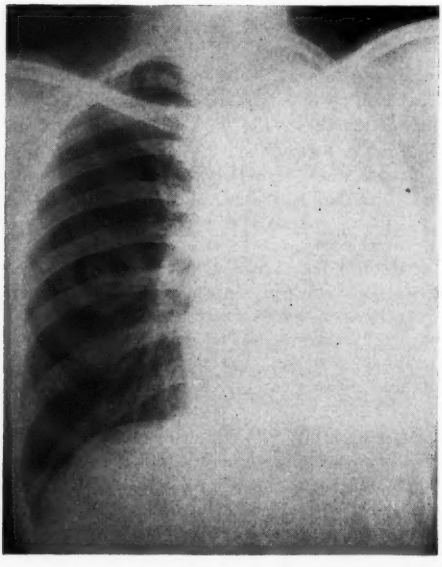


Fig. 2.—Chest roentgenogram on admission to the Massachusetts General Hospital six years after the onset of the disease. A tube can be seen draining an empyema cavity anteriorly.

Roentgenograms of the chest (Fig. 2) showed a normal right lung and complete opacification of the left side of the chest with the exception of a small cavity in the upper anterior portion. The heart shadow was completely obscured by the opacity. Review of the x-ray films led us to believe that the cavity that had been drained was an empyema cavity with a bronchopleural fistula rather than an intrapulmonary cavity because of the thickened pleura around it and the absence of overlying lung markings. When fluid was introduced into the cavity it was coughed up promptly. Further evidence in favor of our opinion was the knowledge that, after cavernostomy, the drainage tract usually becomes free of tubercle bacilli, but after drainage of a tuberculous empyema it usually does not.

An electrocardiogram was characteristic of right ventricular hypertrophy. Cardiac catheterization was carried out and the results are summarized in Table I and Fig. 3. The catheter passed readily through an atrial septal defect into the left atrium. The catheter also passed easily into the right ventricle but could not be advanced into the pulmonary artery.

TABLE I. A COMPARISON OF THE CARDIAC CATHETERIZATION DATA OF PATIENT L. O. COLLECTED PRE- AND POSTOPERATIVELY WITH THE VALUES OBTAINED IN NORMAL SUBJECTS

	M. V. L./ MIN.	O_2 CONS. (C.C./ MIN.)	O_2 CAP. (VOL. %)	ART. O_2 SAT. (%)	A-V DIFF. (VOL. %)	PULM. ART. FLOW L./ MIN./ M^2	SYS-TEMIC FLOW L./ MIN./ M^2	R→L SHUNT L./ MIN./ M^2	P. A. PRES-SURE MM. HG	R. V. PRES-SURE MM. HG	R. A. PRES-SURE MM. HG
Normal	7.5	200	20.0	95	4.0	3.2	3.2	0	30/10	30/0	5
Preoperative Oct. 30, 1953	10.6	299	25.0	78	10.8	1.7	3.1	1.4	-	200/0	5
Postoperative March 8, 1954	5.9	166	14.8	95	4.1	2.4	2.4	0	20/4	83/0	3

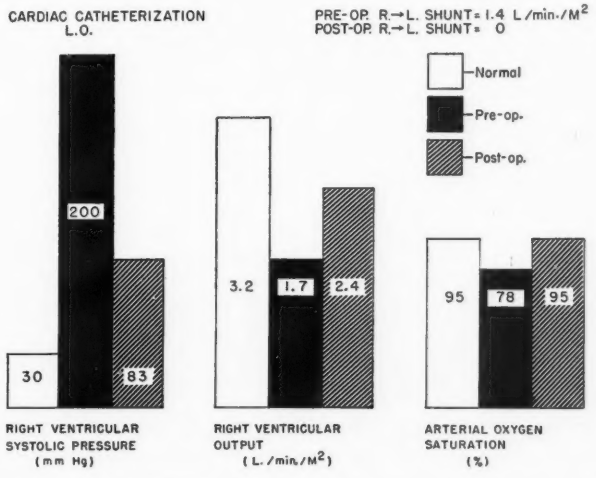


Fig. 3.—Schematic representation of right ventricular pressures, output and arterial oxygen saturation taken pre- and postoperatively and compared with the normal.

In the absence of data concerning the pressure in the pulmonary artery, it was impossible to conclude whether the marked hypertension (200/0) of the right ventricle was due to pulmonary stenosis or to pulmonary vascular disease and pulmonary fibrosis.

Angiocardiographic examination using Diodrast was performed to clarify the diagnosis. This confirmed the presence of an atrial septal defect. No evidence of infundibular stenosis was seen. Valvular stenosis was not demonstrated but could not be excluded. A large main pulmonary artery was visualized. Because of the large atrial septal defect, determinations of circulation time were considered of little value to ascertain the presence of stenosis.

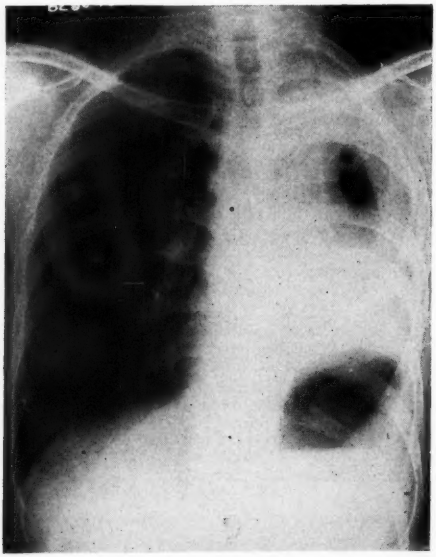


Fig. 4.—Chest roentgenogram taken four months after pulmonary valvulotomy, pneumonectomy, and pleurectomy. A residual intrathoracic cavity is still present.

After some debate, it was decided to explore the heart through the left side of the chest, and if the presumptive diagnosis of pulmonary stenosis was confirmed, to perform a valvulotomy through the artery and then an extrapleural pneumonectomy as described by Sarot.[18] On Nov. 9, 1953, a left posterolateral thoracotomy incision was made and the fifth rib excised. The extrapleural plane was entered, and the left pleural sac and left lung were mobilized with some difficulty. Dissection of the lung and pleural sac from the mediastinum disclosed an enlarged, soft pulmonary artery. There was a well-transmitted systolic thrill consistent with the diagnosis of pulmonary stenosis. Accordingly, the pericardium was opened and a segment of the left pulmonary artery isolated between two traction ligatures. A uterine probe was then inserted through a small incision in the artery, and the presence of pulmonary stenosis was confirmed. The valve orifice was easily identified. It was incised, using a Brock valvulotome passed in a retrograde fashion through the arteriotomy, followed by dilatation using a common-duct-stone grasping forceps. The left pulmonary artery was then ligated and divided and the left pleuropneumonectomy completed. The patient's cardiovascular state remained good throughout, but toward the conclusion of the operation pin-point oozing was apparent within the entire chest cavity and incision. The chest was closed rapidly after insertion of a catheter for drainage.

The early postoperative course was stormy. Constant oozing from the incision and the chest tube persisted despite six transfusions and did not subside until fresh blood was

given. A transitory deficiency in platelets was considered to be the most likely cause of the bleeding. Meanwhile the diabetes was controlled with some difficulty. The pathologic study of the excised lung and pleura demonstrated extensive caseous tuberculosis and tuberculous empyema.

The patient left the hospital two weeks after operation. At this time the incision was well healed. The site of the previous drainage had been closed. The cyanosis and dyspnea were greatly improved.

The patient returned for evaluation four months after the operation. At this time he was not cyanotic and the dyspnea was considerably improved. The sputum was negative for acid-fast organisms. Cardiac catheterization was performed. The results are included in Table I and Fig. 3. Of special interest was the marked fall in the systolic pressure in the right ventricle from 200 to 83 mm. of mercury despite a rise in right ventricular output. The pressure gradient persisting between the right ventricle and the pulmonary artery revealed some degree of pulmonary stenosis.

Arterial oxygen saturation before operation of 78 per cent had risen to a normal value of 95 per cent, evidence that a significant right-to-left shunt through the atrial septal defect was no longer functioning. A chest roentgenogram demonstrated the presence of an interthoracic air- and fluid-filled cavity which continued to drain purulent material positive for tubercle bacilli (Fig. 4).

The patient was last heard from eighteen months after operation. The clinical improvement was well maintained. He had gained weight, and the sputum remained negative. A residual area of infection in the left thoracic cavity had been treated surgically by Dr. Colin A. Ross of Edmonton, Alberta.

SUMMARY

A case of pulmonary stenosis, interatrial septal defect, pulmonary tuberculosis, and diabetes has been presented, to illustrate the feasibility of a combined transarterial valvulotomy and extirpative pulmonary surgery. A satisfactory clinical result was obtained.

REFERENCES

1. Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of the Heart in Which There is Pulmonary Stenosis or Atresia, J. A. M. A. **128**: 189-202, 1945.
2. Brock, R. C.: Pulmonary Valvulotomy for Relief of Congenital Pulmonary Stenosis, Brit. M. J. **1**: 1121-1126, 1948.
3. Sellors, T. H.: Surgery of Pulmonary Stenosis, Lancet **1**: 988, 1948.
4. Dodril, F. D., Hill, E., Gerisch, R. A., and Johnson, A.: Pulmonary Valvuloplasty Under Direct Vision Using Mechanical Heart for Complete By-Pass of the Right Heart in Patient With Congenital Pulmonary Stenosis, J. THORACIC SURG. **26**: 584-597, 1953.
5. Swan, H., Cleveland, H. C., Mueller, H., and Blount, S. G.: Pulmonic Valvular Stenosis: Results and Technique of Open Valvuloplasty, J. THORACIC SURG. **28**: 504-511, 1954.
6. Glover, R. P., Bailey, C. P., O'Neill, T. J. E., Downing, D., and Wells, C. R. E.: Direct Intracardiac Relief of Pulmonary Stenosis in Tetralogy of Fallot, J. THORACIC SURG. **23**: 14-41, 1952.
7. Litwak, R. S., Gadboys, H. L., Scott, G. B., and Ferrara, J. F.: Surgical Approach for Stenotic Lesions of Semilunar Valves by Excision and Cusp Replacement Under Direct Vision, J. THORACIC SURG. **24**: 165-189, 1952.
8. Humphreys, G. H., Powers, S., Fitzpatrick, H., and Lanman, B. M.: Pulmonary Valvulotomy, Surgery **35**: 9-21, 1954.
9. Shumacher, H. B., and Lurie, P. R. Pulmonary Valvulotomy, J. THORACIC SURG. **25**: 173-186, 1953.
10. Deterling, R. A.: Discussion of Shumacher and Lurie.[9]
11. Greene, D. G., Baldwin, E. deF., Baldwin, J. S., Rimmelstein, A., Roh, C. E., and Cournand, A.: Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilation of Pulmonary Artery, Am. J. Med. **6**: 24-40, 1949.

12. Currens, J. H., Kinney, T. D., and White, P. D.: Pulmonary Stenosis With Intact Interventricular Septal Defect, Am. Heart J. **30**: 491-510, 1945.
13. Selzer, D., Carnes, W. H., Noble, C. A., Jr., Higgins, W. H., and Holmes, R. O.: Syndrome of Pulmonary Stenosis With Patent Foramen Ovale, Am. J. Med. **6**: 3-23, 1949.
14. Hawes, J. B.: Heart in Pulmonary Tuberculosis, New England J. Med. **207**: 874-876, 1932.
15. White, P. D.: Heart Disease, ed. 4, New York, 1951, The Macmillan Company, p. 433.
16. Reaud, A.: Diabetes and Tuberculosis, South. M. J. **46**: 248-258, 1953.
17. Ferrara, M. A.: Tuberculous Diabetic Patient, New England J. Med. **246**: 55, 1952.
18. Sarot, I. A.: Extrapleural Pneumonectomy and Pleurectomy in Pulmonary Tuberculosis, Thorax **4**: 173-223, 1949.

ARTERIALIZATION OF THE CORONARY SINUS FOR THE REVASCULARIZATION OF THE HEART IN CORONARY ARTERY DISEASE. MORTALITY STUDY FOLLOWING CIRCUMFLEX CORONARY ARTERY LIGATION

ALVIN A. BAKST, M.D., BROOKLYN, N. Y., JAIME COSTAS-DURIEUX, M.D., PONCE, PUERTO RICO, AND CHARLES P. BAILEY, M.D., PHILADELPHIA, PA.

IN RECENT years, stimulated by the work of Roberts[1] and Beck[2, 3] in the revascularization of the heart for occlusive coronary artery disease, we have been performing aorticocoronary sinus anastomoses. Reports from this clinic have indicated that it is anatomically feasible for aortic blood delivered to the coronary sinus to reach the myocardial capillary bed in retrograde fashion.[7, 8]

During the course of our original experiments on the physiology of the sinus arterialized heart of four to eight weeks' duration, we noted a definite protection afforded to it against ventricular fibrillation following acute occlusion of the left circumflex coronary artery. However, our subsequent experiments on sinus arterialized hearts of six months' duration revealed a significant loss of this protection.

Hahn and Beck[4] have previously noted this protection, which consisted of a reduction in both the mortality and size of infarct following major coronary artery ligation. Eckstein and associates[9, 10] have also noted a definite protection afforded to the acutely arterialized heart following circumflex artery ligation.

The technique for arterialization of the coronary sinus which we used was originally conceived by Pratt[13] and Roberts,[1] and was developed and described by Beck and his associates.[2, 3] It consists of a two-stage operation. At the first stage, through a left-sided thoracic incision, a free segment of external jugular vein is used to anastomose the aorta to the coronary sinus. Three to six weeks later, through a right-sided approach, the coronary sinus is partially ligated over a probe to 2 to 3 mm. Subsequently, the animals are used for the physiologic experiments.

In an effort to study the pathologic effects on the myocardial venous bed of elevating the pressure within the coronary sinus by arterialization, all animals were sacrificed after the physiologic data were obtained.

For the purposes of this comparative mortality report, those animals living for 4 hours following the ligation of the circumflex coronary artery were classified as survivals.

From the Departments of Thoracic Surgery and Physiology, and the Brith Sholem Cardio-Pulmonary Laboratory, Hahnemann Medical College and Hospital, and The Bailey Thoracic Clinic, Philadelphia, Pa.

This work was supported by the Mary Bailey Foundation.

This study was carried out during the tenure (A.A.B.) of a Heart Traineeship sponsored by the National Heart Institute.

Received for publication Dec. 10, 1954.

RESULTS

1. *Group A (Normal Dogs).*—The results in this group may be seen in Table I. In the first 9 dogs, following circumflex coronary artery ligation, ventricular fibrillation ensued within 3 to 30 minutes, with an average time of 13.7 minutes. One dog died after 36 hours. The retrograde blood flow from the distal segment of the ligated and transected circumflex coronary artery ranged from 0.4 to 5.0 c.c. per minute, with an average of 1.7 c.c. per minute. The mean coronary sinus pressure ranged from 2 to 12 cm. of water with an average of 6.1 cm. of water. The coronary sinus pressure of Dog 10 was 4 cm. of water, which was within the range of the average normal, and could not be related to the 36-hour survival time.

TABLE I. MORTALITY IN NORMAL DOGS FOLLOWING LIGATION OF THE CIRCUMFLEX BRANCH OF THE LEFT CORONARY ARTERY

DOG	TIME BETWEEN LIGATION AND DEATH	CAUSE OF DEATH	CORONARY SINUS PRESSURE (CM. H_2O)	RETROGRADE CIRCUMFLEX ARTERY BLOOD FLOW (C.C./MIN.)
1.	30 min.	Vent. Fib.	12	2.2
2.	18 min.	Vent. Fib.	2	4.4
3.	20 min.	Vent. Fib.	5	0.4
4.	3 min.	Vent. Fib.	8.6	0.4
5.	4 min.	Vent. Fib.	8.4	0.5
6.	15 min.	Vent. Fib.	4.6	0.6
7.	16 min.	Vent. Fib.	4.0	1.1
8.	5 min.	Vent. Fib.	7	1.0
9.	12 min.	Vent. Fib.	5	5.0
10.	36 hr.	?	4	1.4
AVERAGE	13.7 min.		6.1	1.7

Vent. Fib. = Ventricular fibrillation.

Inasmuch as we have arbitrarily chosen 4 hours as the statistical basis for our mortality study, and one normal dog lived past this time interval, the mortality rate in our normal series of animals was 90 per cent. However, since at post-mortem examination, the tenth animal obviously had died a cardiac death, without complicating factors, our actual mortality in circumflex arterial ligation was 100 per cent.

2. *Group B (Dogs With Previous Miscellaneous Cardiac Operations).*—The results in this group are tabulated in Table II.

A. In those dogs in which the circumflex branch of the left coronary artery was ligated, three died of ventricular fibrillation within 14 to 20 minutes; one died of cardiac arrest in 17 minutes; one survived for 48 hours; and one survived for 40 days. Retrograde circumflex arterial blood flow ranged from 0.5 to 6.0 c.c. per minute, with an average of 1.9 c.c. per minute. Coronary sinus pressure ranged from 4.0 to 12 cm. of water, and averaged 6.7 cm. of water. The mortality rate in this series of animals was 66 per cent.

B. In the group of dogs in which the left anterior descending artery was ligated at its origin, three died of ventricular fibrillation in 1 to 23 minutes. Two animals lived until they were sacrificed at 40 days. The retrograde blood flow from the distal cut end of the artery ranged from 1.5 to 11.0 c.c.

per minute, with an average of 5.1 c.c. per minute. The coronary sinus pressure ranged from 4 to 10 cm. of water, with an average of 6.6 cm. of water. Thus, in this group of animals, the mortality rate was 60 per cent.

In both groups of animals, there was no demonstrable correlation between coronary sinus pressure and survival following coronary artery ligation. Of the animals in which the left anterior descending artery was ligated, two survived. In both, an accessory left anterior descending artery arose from the circumflex artery (Fig. 1) and coursed downward over the left ventricle parallel to the left anterior descending artery. In both animals the retrograde blood flow from the distal cut end of the anterior descending artery was significantly greater than the normal average.

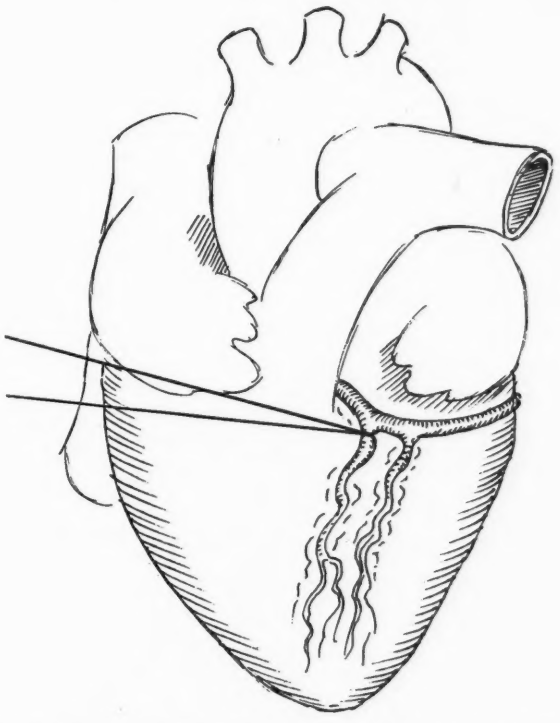


Fig. 1.—An accessory left anterior descending artery is seen to arise from the circumflex coronary artery 0.5 cm. distal to its origin. The accessory vessel courses downward over the left ventricle parallel to the left anterior descending artery, and provides for an abundant amount of intercoronary arterial anastomotic flow.

3. *Group C (Dogs With Coronary Sinus Arterialized for 4 to 8 Weeks).*—The results in this group are tabulated in Table III. In this group, following circumflex coronary artery ligation, two dogs have survived for a prolonged period of time, and six dogs survived from 6 to 96 hours, with an average time of 28 hours. This provides a mortality rate of 20 per cent. It

TABLE II. MORTALITY IN DOGS HAVING HAD PREVIOUS MISCELLANEOUS CARDIAC SURGERY FOLLOWING MAJOR CORONARY ARTERY LIGATION

DOG	TIME ELAPSED FROM LIGATION TO DEATH	CAUSE OF DEATH	CORONARY SINUS PRESSURE (CM. H_2O)	RETROGRADE BLOOD FLOW (C.C./MIN.)	REMARKS
Ligation of the Circumflex Branch of the Left Coronary Artery					
1.	40 days	?	5.4	1.1	Thrombosed Beck; coronary ligation 3 weeks after surgery
2.	20 min.	Vent. Fib.	6.0	1.2	Thrombosed Beck; coronary ligation 3 weeks after surgery
3.	17 min.	Cardiac arrest	23	1.2	Previous atrioseptal defect created under hypothermia in severe congestive failure
4.	20 min.	Vent. Fib.	12	6.0	Thrombosed Beck; coronary ligation 5 weeks after surgery
5.	14 min.	Vent. Fib.	6.4	0.5	Open and close of right auricle under hypothermia
6.	48 hr.	?	4.0	1.4	Thrombosed Beck
Ligation of the Anterior Descending Ramus of the Left Coronary Artery					
1.	10 min.	Vent. Fib.	4	1.8	Right auricle opened under hypothermia
2.	23 min.	Vent. Fib.	7	1.5	Atrioseptal defect created and closed under hypothermia
3.	1 min.	Vent. Fib.	5	No sample	Atrioseptal defect created and closed under hypothermia
4.	40 days	Sacrificed	10	6.2	Atrioseptal defect created and closed under hypothermia; accessory L.A.D. from circumflex coronary artery
5.	40 days	Sacrificed	7.2	11.0	Atrioseptal defect created and closed under hypothermia; accessory L.A.D. from circumflex coronary artery

Vent. Fib. = Ventricular fibrillation.
L.A.D. = Left anterior descending artery.

should be noted that the two animals surviving the procedure had no pleural adhesions and therefore no pulmonary air leaks. Five of the six animals, dying after 6 hours, died of a tension pneumothorax; the sixth died of

TABLE III. MORTALITY IN DOGS WITH CORONARY SINUS ARTERIALIZATION OF ONE TO TWO MONTHS' DURATION, FOLLOWING CIRCUMFLEX CORONARY ARTERY LIGATION

DOG	TIME BETWEEN ARTERIAL LIGATION AND DEATH	CAUSE OF DEATH	CORONARY SINUS PRESSURE (CM. H_2O)	RETROGRADE BLOOD FLOW (C.C./MIN.)
1.	24 hr.	Tension pneumothorax	45	9.6
2.	10 hr.	Tension pneumothorax	80	9.0
3.	24 hr.	Hemorrhage	60	11.0
4.	1 hr. (3 min. after the graft clamped)	Cardiac arrest	36	12.0
5.	2 hr. (5 min. after the graft clamped)	Ventricular fibrillation	60	12.0
6.	96 hr.	Pneumothorax and empyema	71	10.0
7.	Survived	No pleural adhesions present	64	18.0
8.	Survived	No pleural adhesions present	59	10.0
9.	6 hr.	Tension pneumothorax	68	14.0
10.	12 hr.	Tension pneumothorax	70	16.0

hemorrhage from the transected coronary artery. Two animals died within 6 hours. In both, the heart beat well for 1 to 2 hours following circumflex coronary artery ligation. In both, the vein graft was occluded, for the collection of data, after which both expired of ventricular fibrillation. It was impressive to note the rapid onset of ventricular fibrillation following occlusion of the graft in hearts which had been beating forcefully for long periods of time prior to the occlusion of the graft.

Retrograde blood flow ranged from 9.0 to 18.0 c.c. per minute, with an average of 12.2 c.c. per minute. Mean coronary sinus pressure ranged from 36 to 80 cm. of water, with an average of 61 cm. of water. It is interesting to note that there was apparently no relationship between the mortality rate and either the mean coronary sinus pressure or the retrograde circumflex arterial blood flow.

4. *Group D (Dogs With Coronary Sinus Arterialized for Six Months).*—The results of this group are tabulated in Table IV. In this group, following circumflex coronary artery ligation, only two dogs survived for 4 hours before sacrifice. Four dogs died of ventricular fibrillation within 1 hour of arterial ligation, with an average time of 94 minutes. This provides a mortality rate of 66 per cent. Retrograde circumflex arterial blood flow ranged from 3 to 18 c.c. with an average of 8.3 c.c. per minute. Mean coronary sinus pressure ranged from 85 to 100 cm. of water, with an average of 90 cm. It is again of interest to note that there was no obvious relationship between the survival rate and either the mean coronary sinus pressure or the retrograde circumflex arterial blood flow.

TABLE IV. MORTALITY IN DOGS WITH CORONARY SINUS ARTERIALIZATION OF SIX MONTHS' DURATION, FOLLOWING CIRCUMFLEX CORONARY ARTERY LIGATION

DOG	TIME BETWEEN ARTERIAL LIGATION AND DEATH (MIN.)	CAUSE OF DEATH	CORONARY SINUS PRESSURE (CM. H_2O)	RETROGRADE BLOOD FLOW (C.C./MIN.)
1.	30	Vent. Fib.	85	18
2.	240	Sacrificed	90	9
3.	240	Sacrificed	90	4
4.	20	Vent. Fib.	85	7.5
5.	12	Vent. Fib.	90	3
6.	20	Vent. Fib.	100	8
AVERAGE	94		90	8.3

Vent. Fib. = Ventricular fibrillation.

DISCUSSION

In these experiments on the normal dogs and those in which the coronary sinus had been arterialized for 4 to 8 weeks, we were originally impressed by an apparent protection afforded the heart by coronary sinus arterialization, against the onset of ventricular fibrillation following major coronary artery ligation. This impression was quickly dispelled by our subsequent experiments on animals in which the coronary sinus had been arterialized for 6 months. In the group of normal animals, and in those having had previous miscellaneous cardiac operations, we found it imperative to expedite the collection of data, before ventricular fibrillation ensued. After the coronary sinus had been arterialized for 4 to 8 weeks, however, the heart continued to

beat in vigorous uninterrupted fashion following circumflex coronary artery ligation. We soon learned that in these animals we could proceed more deliberately in securing our blood samples, providing the graft was functioning. Once the graft was occluded, data had to be obtained with dispatch, lest the heart fibrillate. In two dogs in which the heart beat well for 1 and 2 hours, respectively, following ligation of the circumflex artery, ventricular fibrillation ensued within 5 minutes of the occlusion of the graft. This observation could not be substantiated in our subsequent experiments on animals in which the coronary sinus had been arterialized for 6 months. In this group, though we had more time to collect data than in the normal group, we were singularly unimpressed by the afforded protection to the heart against ventricular fibrillation by the presence of the graft. These findings have been previously described by others. Hahn and Beck[4] ligated the descending ramus of the left coronary artery in normal and in sinus arterialized animals with essentially similar results. These investigators noted a 70 per cent mortality following left anterior descending ligation in the normal dogs, and the myocardial infarcts were extensive in those surviving ligation. In sinus-arterialized dogs, the mortality fell to 11 per cent. In these dogs a gross infarct was absent in more than one-half of the specimens, and in the remaining ones the myocardial destruction was limited to small areas. In ten dogs which had had previous unsuccessful sinus arterialization with subsequent thrombosis of the graft, ligation of the anterior descending artery again resulted in a 70 per cent mortality.

Eckstein and co-workers,[9-10] in experiments on acutely prepared sinus arterialized animals, demonstrated an immediate protection to the heart against ventricular fibrillation following circumflex coronary artery ligation. In those experiments, the animal was deemed a survival if it lived for more than 60 minutes following circumflex coronary artery ligation. In a group of normal control animals, seven died of ventricular fibrillation within an average time of 8.9 minutes. Three lived more than 60 minutes (one developed ventricular fibrillation in 67 minutes). In a group of acutely prepared sinus arterialized animals, none died within the prescribed 60 minutes. One died in 62 minutes of cardiac arrest, and one died of ventricular fibrillation in 3 hours.

Eckstein's experiments suggest a protection to the heart against ventricular fibrillation in acutely prepared sinus arterialized animals. This suggests an immediate protection explained by the retrograde perfusion of the myocardial capillary bed without the development of increased intercoronary arterial anastomotic flow. In our previous work,[11] in addition to the retrograde perfusion of the myocardial capillary bed with arterialized blood introduced into the coronary sinus, we were able to demonstrate a definite increase in the intercoronary anastomotic flow.

Our mortality rates in the first portion of these experiments were essentially similar to those reported by Hahn and Beck. Ligation of the circumflex coronary artery resulted in a 90 per cent mortality rate in normal

animals. The average time of onset of ventricular fibrillation was 13.7 minutes following ligation of the artery. The length of elapsed time prior to the onset of ventricular fibrillation was not apparently related to either the coronary sinus pressure, or the retrograde blood flow from the distal end of the transected circumflex coronary artery. In those dogs which had had previous miscellaneous cardiac surgery, circumflex coronary artery ligation was associated with a 66 per cent mortality within 20 minutes due to ventricular fibrillation. When the left anterior descending artery was ligated in those animals having had previous miscellaneous cardiac surgery, the mortality rate was 60 per cent. Of the two animals surviving anterior descending ligation, both had accessory anterior descending vessels arising from the circumflex branch of the left coronary artery. The accessory vessel arose 0.5 cm. to the left of the anterior descending artery, and coursed over the left ventricle to the apex parallel to it (Fig. 1). In both animals, coronary sinus pressure was slightly higher than average, but within normal limits. However, in both animals the retrograde arterial flow from the distal cut end of the vessel was significantly increased above the normal average (see Table II). This increased arterial backflow is probably a measure of a more abundant intercoronary arterial anastomotic flow, which, in turn, explains the survival of these animals following anterior descending coronary ligation.

The mortality rate following left anterior descending coronary artery ligation in our small series was 60 per cent. The mortality rate reported by Hahn and Beck in their series of animals was 70 per cent. It is interesting to speculate whether the surviving animals in their series also had such an anomalous accessory left anterior descending artery.

The mortality rate in the animals in which the coronary sinus had been arterialized for 4 to 8 weeks was 20 per cent. Two of these animals in which the pleural cavity was free from pleural adhesions survived circumflex coronary artery ligation for 3 months until sacrificed. All of the six animals in which lung leaks were produced died of tension pneumothorax, empyema, or hemorrhage. Two animals died within 2 hours, one of ventricular fibrillation and the other of cardiac arrest. It is interesting to note that, in both, the heart beat regularly and forcefully until the vein graft was clamped. In both animals, ventricular fibrillation ensued shortly after the vein graft was occluded.

In those animals in which the coronary sinus had been arterialized for 6 months, the mortality rate following circumflex coronary arterial ligation was 66 per cent. The average time elapsing between arterial ligation and death was 94 minutes. It should be realized that in the normal group of animals, although the mortality rate following ligation of the circumflex coronary artery was 90 per cent, the figure fell to 66 per cent in those animals in which previous miscellaneous cardiac operations had been performed. Thus, in the group of animals in which the coronary sinus had been arterialized for 6 months, the mortality rate following circumflex coronary arterial ligation was unchanged from that subsequent to circumflex ligation in a

group of normal animals having previously had miscellaneous cardiac procedures. Moreover, although we had noticed a protection afforded to the heart after the coronary sinus had been arterialized for 1 to 2 months, we were unable to repeat and confirm these observations in subsequent experiments on the 6-month-group of animals. In this latter group, we did note that a longer period of time elapsed between the ligation of the circumflex artery and ventricular fibrillation. We were unable to demonstrate, however, that the occlusion or the opening of the vein graft had any effect upon the speed of onset of ventricular fibrillation. In the two animals which survived arterial ligation, the vein graft had been clamped for the last 2 hours prior to sacrifice. It was our impression and general conception that arterialization of the coronary sinus originally provided for a retrograde perfusion of the myocardial bed, in addition to stimulating the intercoronary arterial anastomotic flow. This was demonstrated in our original experiments on the group of animals in which the coronary sinus had been arterialized for 1 to 2 months. In the group of animals in which the coronary sinus was arterialized for 6 months,[12] although we were able to confirm a fivefold increase in the intercoronary arterial anastomotic flow, we were unable to demonstrate the presence of any retroperfusion of the myocardial capillary bed. This led us to believe that although the graft stimulated an increase in the intercoronary anastomoses, something happened between the second and sixth month which prevented the retroperfusion of the myocardium. We were impressed by the obvious ineffectiveness of the opening or the clamping of the vein graft upon the protection of the heart against ventricular fibrillation. We have examined a group of these hearts pathologically, and have noted a striking intimal proliferation, with thrombosis and occlusion of the major tributaries of the coronary sinus. The occlusion of these major venous tributaries is adequate explanation for the loss of retroperfusion of the myocardial capillary bed. A complete exposition of these pathologic findings will be presented in a subsequent report.

Thus, in our experiments on major coronary artery ligation in normal animals, in those which have had previous miscellaneous cardiac surgery, and those in which the coronary sinus had been arterialized, we were unable to demonstrate any significant prolonged protection against ventricular fibrillation afforded to the heart by arterialization of the coronary sinus.

SUMMARY AND CONCLUSIONS

1. The circumflex coronary artery was ligated in normal dogs, with a 90 per cent six-hour mortality rate and an eventual 100 per cent mortality rate.

2. Ligation of the circumflex coronary artery in dogs which have had previous miscellaneous cardiac surgery resulted in a 66 per cent mortality rate. The 33 per cent survival rate was not apparently related to either coronary sinus pressure or the amount of retrograde blood flow from the distal cut end of the ligated coronary artery.

3. Ligation of the left anterior descending artery in similar dogs resulted in a 60 per cent mortality rate. Two survivors demonstrated an accessory

left anterior descending artery arising from the circumflex coronary artery. This accessory vessel probably accounted for an increase in the intercoronary arterial anastomotic flow which was adequate to protect the heart against ventricular fibrillation.

4. Ligation of the circumflex branch of the left coronary artery in animals in which the coronary sinus was arterialized for 1 to 2 months resulted in a 20 per cent mortality. It is of interest that in the two dogs that died, the heart beat well for 1 and 2 hours, respectively, following circumflex artery ligation. Ventricular fibrillation ensued in both animals within 5 minutes of occlusion of the graft. We were originally impressed by the protection afforded by the anastomosis of the aorta to the coronary sinus.

5. Ligation of the circumflex branch of the left coronary artery in animals in which the coronary sinus had been arterialized for 6 months produced a 66 per cent mortality. In this group, we were unable to demonstrate any significant protection against ventricular fibrillation afforded by arterialization of the coronary sinus.

6. This loss of protection was accompanied by a loss of retroperfusion of the myocardium, which was explained by a marked intimal proliferation and thrombosis within the major venous tributaries of the coronary sinus.

REFERENCES

1. Roberts, J. T., Browne, R. S., and Roberts, G.: Nourishment of the Myocardium by Way of the Coronary Veins, Fed. Proc. **2**: 90, 1943.
2. Beck, C. S.: Revascularization of the Heart, Ann. Surg. **128**: 854, 1948.
3. Beck, C. S., Hahn, R. S., Leighninger, D. S., and McAllister, F. F.: Operation for Coronary Artery Disease, J. A. M. A. **147**: 1726, 1951.
4. Hahn, R. S., and Beck, C. S.: Revascularization of the Heart. A Study of Mortality and Infarcts Following Multiple Coronary Artery Ligation, Circulation **5**: 801, 1952.
5. Hahn, R. S., and Kim, M.: Revascularization of the Heart. Histologic Changes After Arterialization of the Coronary Sinus. Circulation **5**: 810, 1952.
6. Hahn, R. S., Kim, M., and Beck, C. S.: Revascularization of the Heart. Observations on the Circulation Following Arterialization of the Coronary Sinus, Am. Heart J. **44**: 772, 1952.
7. Bailey, C. P., Geckeler, G. D., Truex, R. C., Likoff, W., Antonius, N. A., Angulo, A. W., Redondo-Ramirez, H. P., and Neptune, W: Arterialization of the Coronary Sinus, J. A. M. A. **151**: 441, 1953.
8. Bailey, C. P., Truex, R. C., Angulo, A. W., Geckeler, G. D., Likoff, W., Antonius, N. A., and Neptune, W.: The Anatomic (Histologic) Basis and Efficient Clinical Surgical Technique for the Restoration of the Coronary Circulation, J. THORACIC SURG. **25**: 143, 1953.
9. Eckstein, R. S., Smith, G., Eleff, M., and Demming, J.: The Effect of Arterialization of the Coronary Sinus in Dogs on Mortality Following Acute Coronary Occlusion, Circulation **6**: 16, 1952.
10. Eckstein, R. S., Hornberger, J. C., and Sano, T.: Acute Effects of Elevation of Coronary Sinus Pressure, Circulation **7**: 422, 1953.
11. Bakst, A. A., Costas-Durieux, J., Goldberg, H., and Bailey, C. P.: Protection of the Heart by Arterialization of the Coronary Sinus. II. Coronary Flow in Dogs with Aorticocoronary Sinus Anastomosis. J. THORACIC SURG. **27**: 442, 1954.
12. Bakst, A. A., Adam, A., Goldberg, H., and Bailey, C. P.: Arterialization of the Coronary Sinus in Occlusive Coronary Artery Disease. III. Coronary Flow in Dogs With Aorticocoronary Sinus Anastomosis of Six Months' Duration, J. THORACIC SURG. **29**: 188, 1955.
13. Pratt, F. H.: The Nutrition of the Heart Through the Vessels of Tebesius and the Coronary Veins, Am. J. Physiol. **1**: 86, 1898.

A TECHNIQUE FOR THE EXPERIMENTAL CREATION OF AORTICOPULMONARY FISTULA

MORLEY COHEN, M.D.,* HERBERT E. WARDEN, M.D.,** AND C. WALTON LILLEHEI, M.D.
MINNEAPOLIS, MINN.

CONGENITAL aorticopulmonary fistula, although physiologically and clinically related to patent ductus arteriosus, is on the whole a much rarer condition. Gasul, Fell, and Casas[1] in reporting a case of this anomaly in 1951, indicated that only twenty-four cases had been previously recorded in the literature. Gibson[2] and Spencer[3] have discussed the clinical syndrome associated with this lesion. Other recorded interest[4] in this problem has concerned the development of methods for surgical closure of this abnormal shunt.

From a clinical and physiological viewpoint, the term aorticopulmonary fistula is probably most suitable. Other descriptive terms that have been applied are aortic-pulmonary window and aortic septal defect. Because this anomaly produces alterations in circulatory dynamics which parallel those of patent ductus arteriosus (although usually of a more severe degree), and is usually diagnosed clinically as patent ductus arteriosus, it would seem more purposeful to retain the term aorticopulmonary fistula.

The embryogenesis of these fistulas is probably related to arrested development of the aortic septum between the fifth and eighth weeks of intrauterine life. Normally the truncus arteriosus undergoes separation into separate channels by the growth of the aortic septum. The failure of growth or fusion of the anlagen of the aortic septum may result in a partial persistence of the truncus arteriosus into the postnatal period, with a resulting aortic septal defect. Depending on the degree of arrested growth, windowlike communications between the aorta and pulmonary artery result, varying from small to large openings located from a few millimeters to several centimeters distal to the valve cusps. Typically the defect is about 1.5 cm. in diameter and without significant length. Surgical attempts at closure of these fistulous communications have been fraught with the dangers of uncontrollable hemorrhage due to their proximity to the valve cusps of both the pulmonary artery and aorta. Although a few successful cases have been reported,[4-7] most cases have been left untreated.

Scott and Sabiston,[4] in 1953, reported on an experimental method for the creation and closure of aorticopulmonary fistula. This technique involved

From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn.

Supported by Research grants from: (1) Graduate School, University of Minnesota, (2) Minnesota Heart Association, (3) Life Insurance Medical Research Fund, and (4) National Heart Institute of the United States Public Health Service (H-830).

Received for publication Dec. 13, 1954.

*Life Insurance Medical Research Fellow.

**National Heart Trainee, United States Public Health Service.

the dissection of the base of the aorta and pulmonary artery and direct suture anastomosis of these two vessels after applying Potts ductus clamps. In this way a fistula was created which lay about 1 cm. from the aortic valve and even less from the pulmonary cusps. In their experience, fistulas over 6 mm. in diameter did not permit a long-term survival, death resulting from pulmonary edema in four to ten days. Closure of these fistulas was successfully accomplished in five of twelve long-term survivors, by dissection of the fistula, reapplication of Potts clamps with division, and oversewing of the previous anastomosis.

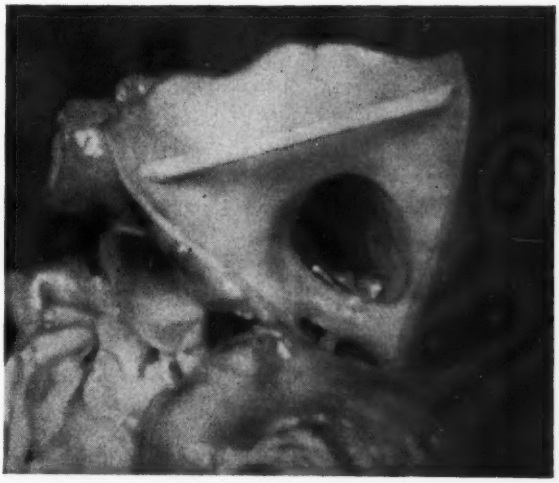


Fig. 1.—Photograph of a congenital aorticopulmonary septal defect viewed through the opened aorta. The patient was an 11-year-old girl, who suffered from repeated episodes of pneumonia and had suffered, five years previously, an attack of bacterial endocarditis which was controlled with antibiotics. This patient expired at surgery due to a tear incurred (indicated by the probe) as an attempt was made to dissect the inferior margin of the fistula. Note similarity with experimental defects.

It is our opinion that the technique of Scott and Sabiston is sound. However, a review of the pathologic anatomy of this defect reveals that in some aspects a fistula created by the suture technique may not be comparable to many cases of aorticopulmonary window seen clinically. When the levels of the cusps of the pulmonary artery and the aorta are observed in the transverse plane, it can be seen that the aortic cusps lie approximately 0.5 to 1 cm. below those of the pulmonary artery. However, aortic septal defects seen clinically are frequently located in such fashion as to be equidistant from both sets of cusps, and may, in fact, include a portion of the cusp sinuses. In these low-lying defects, dissection of the inferior margin of the fistula is virtually impossible. Such a case was described by Scott[4] in which an attempt at proximal dissection was unsuccessful. Similar cases in which the fistulas abutted on the arterial valves have been reported by Dodds and Hoyle[8] and have been encountered on two occasions in our experience (Fig. 1).

METHOD

With these principles in mind, a series of experiments were carried out in an attempt to produce in dogs a fistula comparable to that seen clinically in aortic septal defects so that techniques for closure might be tested experimentally. Preliminary attempts consisted in the placement of a stab wound at the base of the heart where the walls of the pulmonary artery and aorta are in apposition. Although it was possible to create a fistula in this way, there was moderate to severe dissection of blood between the vessels, and the fistula almost invariably closed in twenty-four to ninety-six hours. This experience had occurred also in the hands of others.[4] Subsequently the following method was evolved.

Utilizing healthy mongrel dogs of unselected weight, anesthesia was induced employing intravenous Nembutal (25 mg. per kilogram body weight) following preoperative medication with morphine sulfate (4 mg. per kilogram body weight). Respiration was maintained using a mechanical insufflator and a cuffed endotracheal tube. The animal was positioned with the left chest uppermost, and it was entered, under sterile conditions, through a short incision in the fourth interspace. The pericardium was opened, and the intrapericardial fat pad overlying the base of the aorta and pulmonary artery was dissected away (Fig. 2, Stage I). By gentle retraction of the pulmonary artery, one is readily able to develop the plane between these two vessels down to the root of the aorta. When this point is reached, the origin of the right and left coronary arteries is clearly visualized. A wafer of polyvinyl (Ivalon) sponge, about 0.5 mm. in thickness and 2.0 cm. square, which had been previously soaked in a 4 per cent solution of diacetyl phosphate, was then placed between the root of the aorta and the pulmonary artery; if desired the sponge may be secured by a single stitch placed above it between the adventitial layers of the two vessels to ensure against possible displacement. The pericardium was loosely approximated and the chest closed. Postoperatively, 300,000 units of penicillin and 0.5 Gm. of streptomycin were given for three days. The animals were allowed to recover for a period of about six weeks after which time the fistulas were created at a second operation.

For the second stage, the left chest was reopened through the fourth interspace utilizing the same premedication and anesthesia. The pericardium was opened and retracted with stay sutures. A purse-string suture of 4-0 black silk on a fine Atraumatic needle was placed in the anterior wall of the pulmonary artery, just above the pulmonary valve (Fig. 2, Stage II). The purse-stringed area was then excluded from the arterial lumen by a Satinsky or a curved Potts ductus clamp and incised. A commercial cork-borer, 4 to 11 mm. in diameter, was then introduced into the excluded segment of the pulmonary artery; and while an assistant controlled the purse-string, the clamp was removed to permit the borer to enter the pulmonary artery. Blood loss during this maneuver was negligible, and gentle traction on the purse string controls any further bleeding around the borer. The exposed end of the borer is capped with a cork or held with the finger to prevent bleeding. The heart tolerates this manipulation well, and there is no necessity for haste

At this point the index finger of the left hand is introduced into the transverse sinus to act as a guide. Using a rotary motion a defect is then punched out between the contiguous, now firmly adherent walls of the pulmonary artery and aorta. If one keeps in mind the fact that the aortic cusps are lower, the borer can be angled inferiorly so as to place the defect in almost

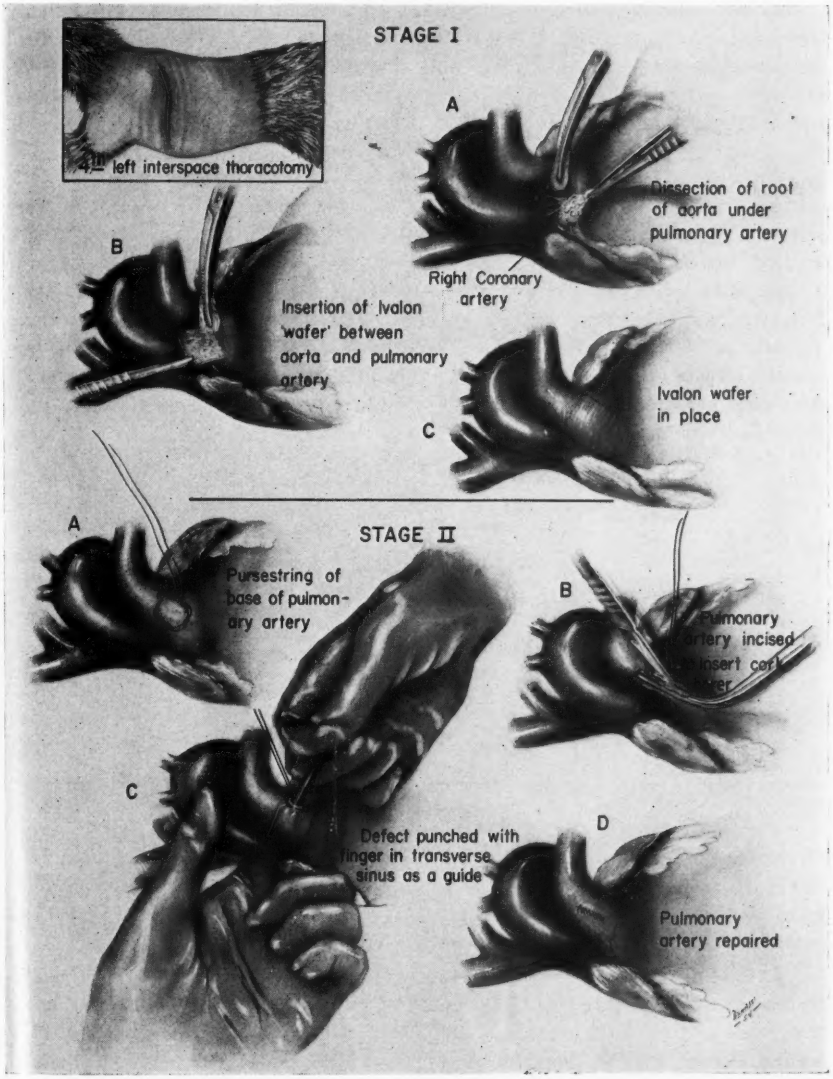


Fig. 2.—Schematic diagram outlining method of creating aorticopulmonary fistulas in two stages. (See text.)

identical positions just above the valve cusps of each vessel. The finger in the transverse sinus acts as a useful guide and greatly aids in the control of the borer. The creation of the defect can be recognized by the immediate appearance of a marked thrill or by momentarily raising the finger from the exposed end of the borer to allow bright red aortic blood to spurt from the borer shaft. The heart usually manifests a tachycardia as soon as the shunt is created. The cork-borer was then carefully withdrawn and the Potts clamp reapplied. A short running suture of 6-0 silk served to close the incision in the pulmonary artery. The chest was then closed, and the animals were observed twice weekly. Murmurs were invariably audible with the stethoscope, and frequently a pronounced thrill could be palpated.

RESULTS

Following some preliminary trials by other methods, nine animals were subjected to the creation of aorticopulmonary fistula by the technique described. As had been the experience of Scott and Sabiston, defects over 5 mm. in diameter were not tolerated, the animals dying of acute heart failure either immediately or early in the postoperative period. In those animals in which the defect was 5 mm. or less, the fistula occasioned no untoward effects and at sacrifice showed no tendency to heal over. The results following creation of aortic-pulmonary shunts in these nine animals are indicated in Table I.

TABLE I. PRODUCTION OF AORTICOPULMONARY FISTULAS

DOG NO.	DEFECT SIZE (MM.)	RESULT
1003	12	Excellent thrill followed by acute cardiac dilatation and arrest within minutes
959	11	Good thrill followed by cardiac dilatation and fibrillation within minutes
862	11	Died 48 hours; heart failure; defect open
957	8	Died 37 days; heart failure; defect open
871	6	Died 9 days; intrapericardial rupture of fistula with cardiac tamponade
496	5	Died 3½ months; distemper; defect open
774	4	Sacrificed 5 months; defect open
29	5	Sacrificed 3½ months; defect open
36	4	Died 4 months; defect open; endocarditis

Photographs of some of these defects are shown in Figs. 3 and 4. Some of these animals, after a period of six weeks, were injected with betahemolytic streptococci in order to compare the susceptibility to endocarditis of these fistulas with those placed elsewhere in the peripheral circulation.[7, 8] This comparison will be the subject of a separate report.

In a few animals, mean pressure studies utilizing a citrate manometer were carried out in the right ventricle and pulmonary artery before the defect was made (at the first stage), immediately after the defect was made (at the second stage), and at the time of sacrifice. These were obtained, utilizing a No. 18 needle, by direct puncture of the respective chambers. In addition, in order to obtain objective evidence of the shunt in two animals, Van Slyke

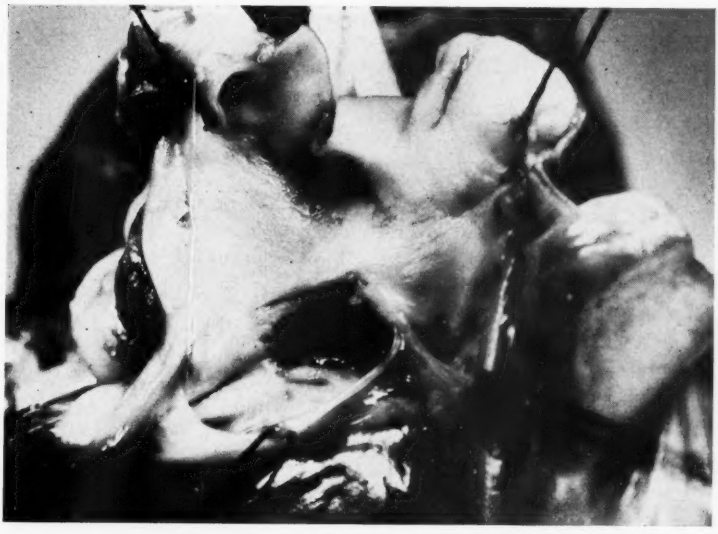


Fig. 3.—Dog No. 957. Eight mm. defect viewed from the aortic side. Animal died of heart failure. Note proximity to aortic leaflets.

Fig. 4.—Dog No. 29. Five mm. defect open at three and one-half months. Note the proximity to aortic cusps and origins of the coronary arteries similar to the congenital variety (Fig. 1).

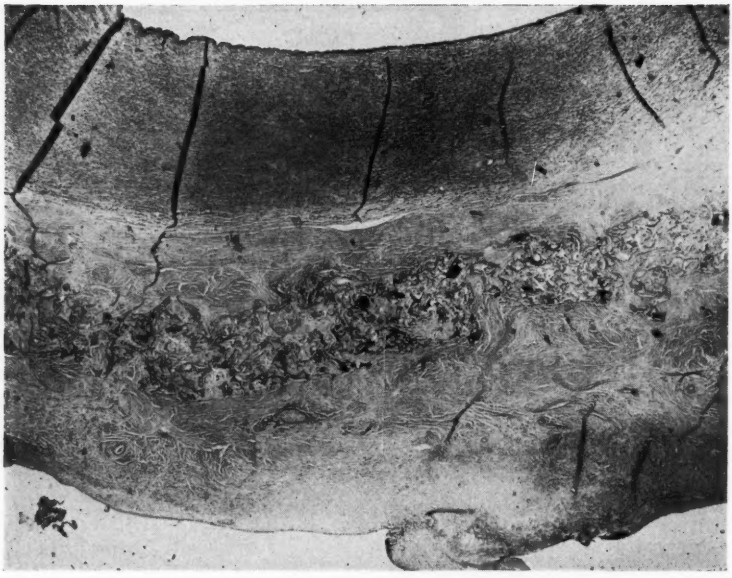


Fig. 5.—Low-power photomicrograph showing the firm adherence of aorta (above) and pulmonary artery (below). The Ivalon sponge is visible between the two vessels. (×75; reduced ⅕.)

Fig. 6.—High-power photomicrograph showing dense fibroplasia which has filled the interstices of the Ivalon sponge. (×400; reduced ⅕.)

determinations of oxygen content were carried out on samples drawn simultaneously from the aorta, right ventricle, and the bifurcation of the pulmonary artery. No true estimate of the magnitude of these shunts can be calculated from these figures as the pulmonary artery samples were not true mixed specimens. However, they did provide a definite indication of the presence of left to right shunts. These oxygen contents and pressure values are indicated in Table II.

TABLE II. HEMODYNAMIC ALTERATIONS OF AORTICOPULMONARY FISTULAS

	PRESSURE (CM. OF CITRATE*)						OXYGEN CONTENT (VOLS. PER CENT) AT SACRIFICE		
	AT 1ST. STAGE		AT 2ND. STAGE		AT SACRIFICE				
DOG NO.	RT. VENT.	PUL. ART.	RT. VENT.	PUL. ART.	RT. VENT.	PUL. ART.	AORTA	RIGHT VENTRICLE	PULMONARY ARTERY
29	20	22	22	29	18	21.5	15.36	8.54	11.71
774	12	12	—	—	16	18	16.84	10.04	13.01
36	14	16	16	18	12	12.5	—	—	—

*The thoracic spine was utilized as a baseline, the animal being positioned on its side.

DISCUSSION

Although the altered physiology and principles of surgical treatment of patent ductus are well documented, the same is not true for aortic septal defects. This, in part, has been the consequence of the lack of an experimental preparation similar to the human anomaly. Wherever one is able to develop a plane of dissection proximal to the fistula, division between clamps would likely be the method of choice; however, in the majority of the clinical instances where this defect exists, the lower margin of the fistula cannot be cleared by dissection because it encroaches on the aortic and/or pulmonary valve cusps. In these cases it would appear that a direct vision approach through the dilated pulmonary artery under total venous inflow occlusion might be considered more feasible.

The use of polyvinyl sponge in inducing a firm fibrous union between the origins of both arteries has permitted the blind creation of defects at the level of the respective valve cusps. This sponge is readily invaded by connective tissue (Figs. 5 and 6) and will permit the creation of a clean defect if a razor-sharp cutting instrument is employed. These defects permit a significant (albeit undetermined) shunt and do not demonstrate any tendency to close. Further studies will be made to determine the long-range effects of this type of fistula upon the pulmonary vasculature and to investigate these effects in relation to the volume of the left to right shunt.

The increased susceptibility of the valves of the heart to bacterial endocarditis with significant arteriovenous shunts has been previously documented.[9] The circulation in these experimental animals would appear to be subjected to a significant stress as evidenced by the occurrence of a fulminating bacterial endocarditis following intravenous introduction of small numbers of bacteria which are harmless to animals with a normal circulatory system. The valves most affected were those related to the shunt, particularly the pulmonary valve which in some instances was completely destroyed by engrafted vegetations. These changes are shown in Figs. 7 and 8.

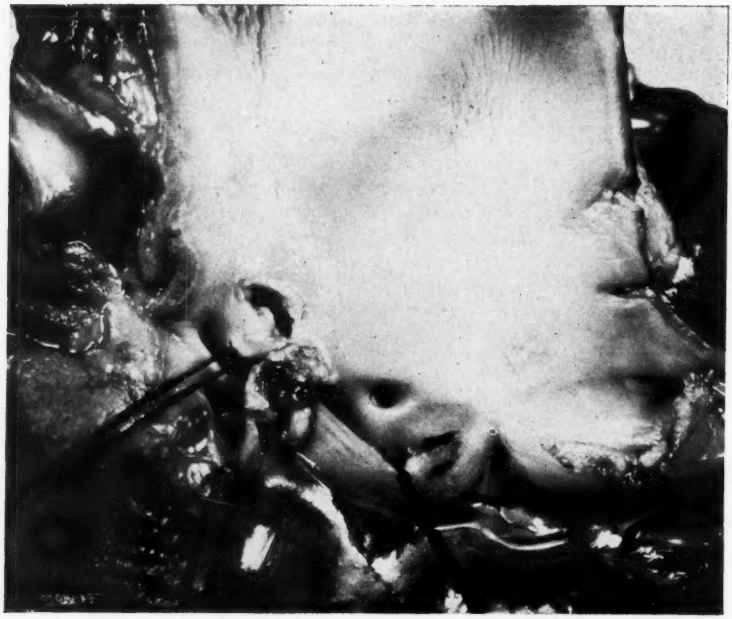


Fig. 7.—Dog No. 36. Four mm. aorticopulmonary defect viewed from aortic side showing bacterial vegetations on the valve cusps.

Fig. 8.—Dog No. 36. Massive vegetations of bacterial endocarditis which have destroyed the pulmonary valve cusps and involved the entire root of the pulmonary artery. The aorticopulmonary fistula is hidden by the vegetations.

The pressure studies recorded in Table II are in keeping with the well-established fact that marked increases in pulmonary flow may occur without producing a significant rise in pulmonary artery pressure, unless or until marked reductions of the pulmonary vascular bed (induced by such means as resection of lung tissue or significant arteriolar changes) have occurred to increase resistance to flow. It is possible, although controversial, that if these shunts were permitted to exist over a period of years, some vascular changes might occur in the pulmonary arterioles with the consequent occurrence of a pulmonary hypertension such as occurs clinically in certain patients with this defect.

SUMMARY

Congenital aorticopulmonary fistula, although not a common congenital heart lesion, continues to present a surgical problem in its repair. Where the lower margin of the defect can be cleared by careful dissection, the division of the shunt between clamps will permit corrective ablation. However, in those instances where the fistula is large and extends to the margin of the arterial valves (which is probably the most common situation), alternate approaches, probably through the pulmonary artery with the circulation temporarily interrupted, become necessary. An experimental method of creating this latter type of defect has been outlined.

REFERENCES

1. Gasul, B. M., Fell, E. H., and Casas, R.: The Diagnosis of Aortic-Septal Defect by Retrograde Aortography, Circulation **4**: 251, 1951.
2. Gibson, S., Potts, W. J., and Langsewich, W. H.: Aortic-Pulmonary Communication Due to Localized Congenital Defect of the Aortic Septum, Pediatrics **6**: 357, 1950.
3. Spencer, H., and Dworken, H. J.: Congenital Aortic Septal Defect with Communication Between the Aorta and Pulmonary Artery, Circulation **2**: 880, 1950.
4. Scott, W. H., Jr., and Sabiston, D. C., Jr.: Surgical Treatment for Congenital Aorticopulmonary Fistula. J. THORACIC SURG. **25**: 26, 1953.
5. Varco, R. L.: Personal Communication.
6. Fletcher, G., Dushane, J. W., Kirklin, J. W., and Wood, E. H.: Aortic Septal Defect: Report of a Case With Surgical Division Along With Successful Resuscitation From Ventricular Fibrillation, Proc. Staff Meet. Mayo Clin. **29**: 285-295, 1954.
7. Gross, R. E.: Surgical Closure of an Aortic Septal Defect, Circulation **5**: 858-863, 1952.
8. Dodds, J. H., and Hoyle, C.: Congenital Aortic Septal Defect, Brit. Heart J. **11**: 390, 1949.
9. Lillehei, C. W., Wargo, D. J., and Hammerstrom, R. N.: Experimental Bacterial Endocarditis and Proliferative Glomerulonephritis, Dis. Chest **24**: 421, 1953.

INTRAPERICARDIAL DISSECTION IN RIGHT PNEUMONECTOMY FOR BRONCHOGENIC CARCINOMA

WILLIAM H. WIERMAN, M.D.,* JOHN W. KIRKLIN, M.D.,** AND F. HENRY ELLIS, JR., M.D.,** ROCHESTER, MINN.

PROOF is not yet available to show that resection more radical than that accomplished by ordinary pneumonectomy offers a better chance for cure of bronchogenic carcinoma than does the latter procedure. There are reasons for believing, from a theoretic standpoint, that such is true. With this in mind, we have executed radical pneumonectomy, as have others, in instances of bronchogenic carcinoma not suitable for lobectomy. In time, data will become available to settle the question as to the advantages of this radical procedure in terms of survival rates.

Meanwhile, it is important to determine the risk of the more extensive operations, and to standardize the techniques. These techniques have been introduced and extended by Allison,[1] by Healey and Gibbon,[2] and by others. We previously outlined our experience with radical left pneumonectomy employing intrapericardial dissection.[3] Herein our experience to date with right pneumonectomy and intrapericardial dissection is detailed, and an appraisal is made of the operative mortality.

ANATOMY

As the pulmonary arteries leave, and the pulmonary veins enter the heart, they receive fibrous projections from the fibrous pericardium, which blend with their adventitia. The superior vena cava, as it enters the pericardium, likewise receives such fibrous expansions. However, as the inferior vena cava enters directly via the central tendon of the diaphragm it does not receive any fibrous reflection.

The serous layer of the parietal pericardium lies on the undersurface of the fibrous pericardium, but at the sites of vessel attachment to the heart the parietal serous layer is reflected to form the visceral serous covering, or epicardium. These lines of serous pericardial reflections form two very short mesenteries: the arterial mesocardium and the venous mesocardium.

The venous serous reflection envelops, with a double membrane, in turn, the inferior vena cava, the right pulmonary veins, the superior vena cava, and the left pulmonary veins. The attachment of these to the posterior parietal pericardium presents the form of an inverted U, and the resultant cul-de-sac lying behind the left atrium is known as the "oblique sinus." The double layer of connecting serous pericardium must be incised both above and below the vessel to allow a ligature to be passed around it.

The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Received for publication Dec. 23, 1954.

*Fellow in Surgery, Mayo Foundation.

**Section of Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.

As the inferior aspects of the pulmonary arteries bulge into the serous sac they receive a serous reflection which must be divided anteriorly and posteriorly to free them completely for ligature.

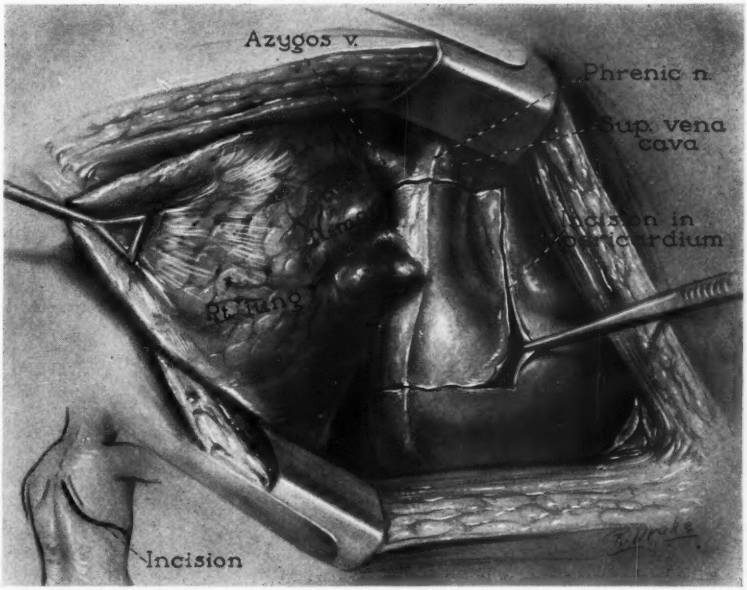


Fig. 1.—Initial stage of right pneumonectomy with intrapericardial dissection. In many cases, the pericardium is incised posterior to the phrenic nerve but when the tumor is encroaching on the pericardium this nerve must be sacrificed.

TECHNIQUE

We have used a posterolateral incision through either the fifth interspace or the bed of the resected sixth rib for right pneumonectomy. In most of our cases, the patient has been on his left side during operation; however, recently we have carried out the identical procedure while the patient was in the prone position. There can be little doubt that the identical operative procedure can be carried out with the patient in either position, although the order of the dissection may have to be altered somewhat. The following description applies when the patient is in the lateral position.

Initially, the entire site of dissection is outlined by incising the mediastinal pleura over the azygos vein and carrying this incision down anteriorly across the superior vena cava and longitudinally opening the pericardium just behind the phrenic nerve. If it is opened well posteriorly in this fashion, there is no difficulty with herniation of the heart through the opening postoperatively. On occasions, however, the carcinoma has invaded anteriorly onto the pericardium in such a way that wider removal is necessary and in these instances the pericardium must be opened anterior to the phrenic nerve as shown in Fig. 1.

A flap of pericardium can then be developed which can be strongly retracted posteriorly to display the superior vena cava above and the lateral aspect of the right atrium below. The superior and inferior pulmonary veins can then be identified intrapericardially and the main right pulmonary artery can be seen to emerge from beneath the superior vena cava. Because of the possible dissemination of tumor emboli through the veins, it has been our practice to secure the veins first whenever possible. The pericardial reflections around the superior pulmonary vein are freed and the vein is doubly ligated on the proximal side flush with the posterior wall of the left atrium and divided between

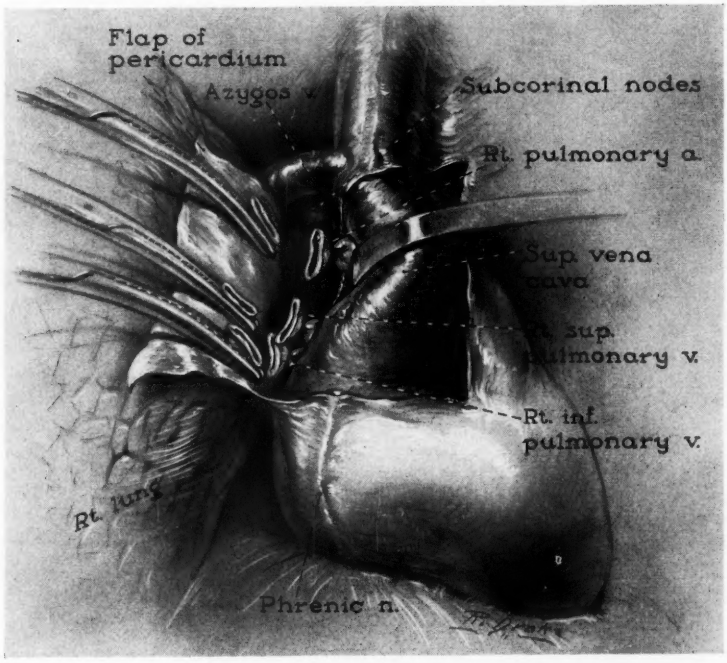


Fig. 2.—The superior and inferior pulmonary veins are secured first. The right pulmonary artery is divided beneath the superior vena cava which is retracted. In practice, all pulmonary vessels are secured by a ligature plus a transfixion ligature.

the distal ligature and a clamp placed more distally. The inferior pulmonary vein is generally secured within the pericardium, although, because of its slightly more posterior location, it is not quite as easily exposed. On occasions when the carcinoma is invading well down onto the pulmonary vein area, it has been possible to place a fine-tooth Potts curved clamp directly on the "diverticulum" of the posterior left atrial wall into which both right pulmonary veins enter. The veins are clamped distally and disconnected from the atrial wall. The resultant defect in the atrium is then oversewn with interrupted silk sutures.

The pulmonary artery is freed from its pericardial reflections beneath the superior vena cava where it is doubly ligated on the proximal side, clamped distally, and divided between the ligatures and the clamp (Fig. 2).

The lung is then retracted anteriorly and the incision of the mediastinal pleura is carried over the azygos vein down, caudally, over the esophagus. The right main bronchus is dissected out in such a way that the subcorynal lymph nodes are peeled down so as to be removed along with the specimen. The bronchus is cut across flush with the trachea and closed with interrupted silk. With traction on the clamp securing the bronchus distally, the lung is elevated, the subcorynal lymph nodes, and the lymph nodes along the proximal reaches of the left main bronchus are dissected away so as to be removed with the specimen.

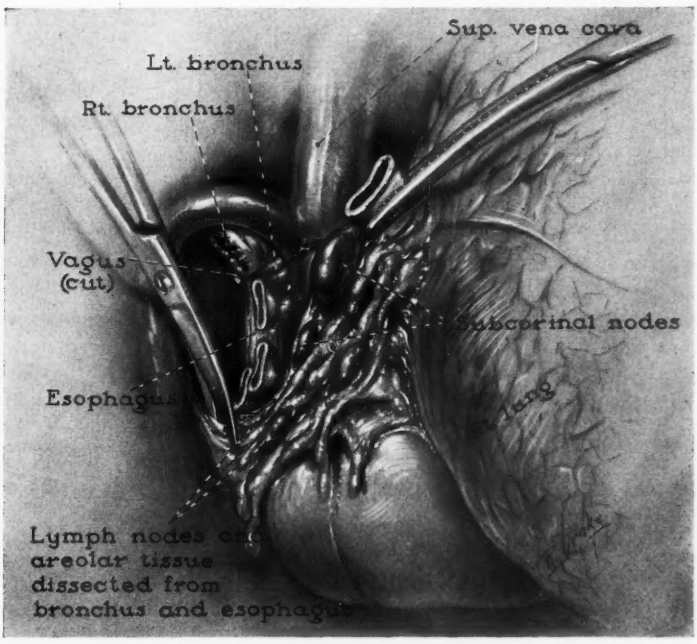


Fig. 3.—The lung is now reflected anteriorly. The subcorynal lymph nodes and nodes along the upper reaches of the left main bronchus are swept down with the specimen. The right bronchus is cut across just distal to the coryna. As the lung is lifted away from the mediastinum, the mediastinal nodes are dissected away en bloc with the specimen.

Likewise, the lymph nodes lying alongside the adjacent esophagus are dissected up to be removed en bloc with the lung and soft tissue and remainder of the mediastinal lymph nodes. The vagus nerve is severed as it emerges from beneath the azygos vein and also severed again distally low in the thorax so that a portion of it is removed with the specimen. As this removal of the specimen progresses, a portion of the pericardium and soft tissue in this region is likewise dissected away (Fig. 3).

At the conclusion of the resection, there remains a defect in the pericardium and a defect in the mediastinal pleura in the region of the hilus of the lung. The left main bronchus, the esophagus, and the aorta can all be seen after this en bloc removal of the lung, a portion of the pericardium, and the mediastinal

lymph nodes. The bronchial stump is carefully covered with mediastinal pleura and soft tissue. The thoracic wall is closed in layers in the usual fashion without drainage.

RESULTS

Right pneumonectomy with intrapericardial dissection and removal en bloc of the mediastinal lymph nodes has been done in 32 cases. During the same period, left pneumonectomy with intrapericardial dissection, as previously described, has been performed on 49 patients, which makes a total of 81 pneumonectomies done by the intrapericardial operation. In this group there have been six deaths during hospitalization, a mortality rate of 7.4 per cent.

In the series of 49 patients who underwent left pneumonectomy, two have died—the case of one patient was reported in our previous communiqué;[3] the other patient died of pulmonary embolism. Four deaths occurred, however, among the 32 patients undergoing right pneumonectomy with intrapericardial dissection, a mortality rate of 12.5 per cent.

Two of these four deaths resulted from respiratory insufficiency in the late postoperative period. One death was due to a massive embolus to the left pulmonary artery occurring on the fifth postoperative day. The fourth patient died as a result of empyema on the right side and subsequent development of a bronchopleural fistula. These data corroborate the impression of others that right pneumonectomy, in general, carries a more significant risk in cases of carcinoma than does left pneumonectomy.

In only one case, namely, that of the patient with empyema and late bronchopleural fistula, could the more radical pneumonectomy have possibly been implicated in the patient's death. There were no other instances of bronchopleural fistula in this series, however, and it is our impression that, in the fatal case reported, the bronchopleural fistula developed after the empyema and was perhaps secondary to it.

It is, of course, impossible as yet to assess the survival rate in these cases. Further time and study will be necessary before it is known whether the more extensive operation results in a higher percentage of survivals.

DISCUSSION

The operative procedure described can be done safely and its use can extend the resectability of carcinoma of the lung. It is not as radical as some procedures described, and we do not deny that a more extensive operation can be done—nor do we deny the possible advantages of such a procedure. This is a safe, rational, aggressive mode of attack on bronchogenic carcinoma. Whether or not it has a more favorable effect on the survival rate than standard pneumonectomy remains to be determined.

REFERENCES

1. Allison, P. R.: Intrapericardial Approach to the Lung Root in the Treatment of Bronchial Carcinoma by Dissection Pneumonectomy, J. THORACIC SURG. **15**: 99-117, 1946.
2. Healey, J. E., Jr., and Gibbon, J. H., Jr.: Intrapericardial Anatomy in Relation to Pneumonectomy for Pulmonary Carcinoma, J. THORACIC SURG. **19**: 864-874, 1950.
3. Kirklin, J. W., and Jampolis, R. W.: Intrapericardial Dissection in Left Pneumonectomy for Bronchiogenic Carcinoma, J. THORACIC SURG. **25**: 280-285, 1953.

METASTATIC MALIGNANT LESIONS OF THE LUNGS TREATED BY PULMONARY RESECTION

A Report of 43 Cases

Robert T. Hood, Jr., M.D.,* Robert P. McBurney, M.D.,** and O. Theron Clagett, M.D.,*** Rochester, Minn.

THE modern surgeon has responded to the therapeutic challenge of malignant disease with increasingly bold attempts to extirpate all discoverable malignant tissue. Wide, en bloc resections of primary growths with partial or total removal of adjacent structures have become accepted surgical procedures for cases of extensive malignancy beyond the hope of cure by lesser surgical measures. Excision of distant metastatic lesions, at first approached as an interesting experiment, has gradually evolved into a defensible but still highly controversial procedure. Pulmonary resection for metastatic lesions probably represents the greatest experience with the surgical excision of distant metastatic lesions. The general acceptance of this procedure, however, awaits a careful assessment of its accrued benefits. These include the palliation afforded, the retardation of the rate of spread of the disease, and the incidence of "cure" effected by the removal of a presumably solitary metastatic lesion. The answers are not to be shortly forthcoming. Experience is still limited and relatively brief. As in all studies involving many types of malignant disease, the extreme variability in the behavior of the individual types of tumors introduces a troublesome complexity. These factors inevitably delay final judgment of pulmonary resection as an established procedure for the treatment of metastatic malignant disease.

In 1950, Seiler, Clagett, and McDonald[1] reviewed the experience at the Mayo Clinic with the treatment of pulmonary metastatic lesions by resection. This report is an extension of that study.

MATERIAL AND METHOD OF STUDY

This study comprises a review of forty-three cases in which pulmonary resection was performed at the Clinic as a definitive procedure for a metastatic tumor of the lung. It does not include cases in which the pulmonary operation was limited to a biopsy of the intrathoracic lesion. Ten of the forty-three cases were previously reported by Seiler, Clagett, and McDonald. The patients of this latter group surviving at the time of their report have been further traced.

Twenty-three of the patients were male and twenty female. The relative similarity of incidence in the sexes is in distinct contrast to the preponderance of males among the patients undergoing pulmonary resection for bronchiogenic carcinoma.

Received for publication Dec. 27, 1954.

*Assistant to the Staff, Mayo Clinic.

**Fellow in Surgery, Mayo Foundation.

***Section of Surgery, Mayo Clinic and Mayo Foundation.

The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

At the Clinic the first pulmonary resection for metastatic malignant lesions was performed in August, 1941, on a patient who had, 3 years previously, undergone nephrectomy for hypernephroma. This study includes all the cases in which removal of metastatic pulmonary lesions was performed prior to 1952. The procedure has been increasingly utilized during recent years. During 1951, pulmonary resection was performed 13 times for metastatic pulmonary lesions.

The ages of the patients at the time of the pulmonary resection varied in this series from 6 to 67 years (Table I). The operations for the primary lesions had been performed between the ages of 6 and 66 years. Fifty-eight per cent of the pulmonary operations were performed on patients in the fifth and sixth decades of life.

TABLE I. AGE OF PATIENTS WITH METASTATIC MALIGNANT LESIONS TREATED BY PULMONARY RESECTION

AGE IN YEARS	INITIAL OPERATION		PULMONARY OPERATION	
	NUMBER	PER CENT	NUMBER	PER CENT
0- 9	2	4.8	1	2.3
10-19	1	2.4	1	2.3
20-29	6	14.3	4	9.3
30-39	8	19.0	6	14.0
40-49	14	33.3	12	27.9
50-59	8	19.0	13	30.2
60-69	3	7.2	6	14.0
Total	42*	100.0	43	100.0

*Excludes one patient without resection of primary growth; see text.

Follow-up studies were obtained on forty-two of the forty-three patients. One patient, a woman whose pulmonary lesion was secondary to an adenocarcinoma of the uterus, could not be located following her dismissal from the Clinic. Among the patients known to be living at the time of this study, the shortest period following operation was 14 months and the longest period 78 months. Follow-up studies applied to eighteen of the patients over a 3-year period and to eleven of them over a 5-year period.

Operations for the primary lesions were all curative in objective, and no detectable malignant tissue remained after completion of the operation. In one case, reported previously by Seiler and associates,[1] a patient with an adenocarcinoma of the colon underwent pulmonary resection prior to removal of the primary growth. In one other case, the secondary nature of the pulmonary lesion was discovered after pathologic examination of the surgically removed lung. The patient succumbed before the location of the primary growth could be discovered. The primary lesion was found at necropsy.* In two patients, the initial growth was treated by roentgen therapy following biopsy rather than by surgical excision.

ANALYSIS OF DATA

Symptoms.—Twenty-four patients did not complain of any significant pulmonary symptoms prior to removal of their metastatic tumors. The commonest complaint among the remainder was a cough, which was present among four-

*Another patient underwent two pulmonary resections for metastatic pulmonary lesions, the first a lobectomy and the second, 37 months later, a local excision.

teen of the patients. In ten of this group, the cough was productive of sputum. Hemoptysis was noted by eight of the patients. Three patients complained of pain, two of dyspnea, and one of wheeze.

In the majority of patients, the onset of pulmonary symptoms was not of itself a factor in the detection of the pulmonary metastasis, since most patients reported regularly for follow-up examinations. However, in twelve patients whose primary lesions had been removed from 3 to 15 years previously, concern about pulmonary symptoms provided the stimulus for seeking medical consultation.

Roentgenologic Characteristics.—All patients in this study presented roentgenologic evidence of a nonobstructive pulmonary mass lesion. The size of the lesions varied from 1 to 7 cm. in diameter. With two exceptions the lesions were solitary. In both of these cases the appearance was that of satellite nodules rather than widely separated or disseminated multicentric lesions. The characteristic lesion was peripheral in location, rather than situated deeply within the lung. It was round rather than oval or irregular in shape. Its border was distinct rather than hazy, its shadow dense, and its consistency homogeneous. Small lesions, naturally, were less likely to present a distinct border and heavy shadow than large lesions. No lesions in this group showed roentgenologic evidence of central necrosis or calcification. Except in two cases, no detectable pulmonary lesion was present at the time of operation for the primary tumor; thus, the appearance of a mass in the lung was prima facie evidence of a growing lesion.

Cytologic Examination of the Sputum.—Many of the patients underwent pulmonary resection prior to the establishment of cytologic examination of the sputum as a standard procedure, so that the number of patients studied by this means was necessarily small. Eleven patients had at least one examination of the sputum for malignant cells. Atypical cells were found in one patient. In two cases, an unequivocal diagnosis of malignant cells was reported. The results of examination for eight patients were negative.

Bronchoscopic Examination.—For many years at the Clinic it has not been customary to perform bronchoscopy uniformly on patients because of the sole finding of a pulmonary lesion on the roentgenogram. Since peripheral lesions rarely can be visualized by bronchoscopy, this procedure, in the absence of other indications for bronchoscopy, was not performed on the majority of these patients.

Preoperative bronchoscopy was performed on eleven patients, only three of whom failed to show some abnormality related to their metastatic lesion. In five cases, tissue obtained by biopsy was demonstrated to be malignant. The tissue from another mass showed only inflammatory changes. In another patient, the right lower lobe bronchus was narrowed. Bronchoscopy revealed blood coming from the affected lobe in another.

Pathologic Nature of Primary Tumor.—The metastatic tumors encountered in this group of patients arose from a wide variety of primary growths (Table II). Thirty-two of the tumors were classed as carcinomas. This group included the cases of teratoma of the testis, mixed tumor, and hemangioma. Eleven of

TABLE II. TYPE OF PRIMARY TUMOR FOR WHICH PULMONARY RESECTION OF THE METASTATIC LESION WAS CARRIED OUT

TYPE OF PRIMARY TUMOR		CASES
Carcinoma		32
Adenocarcinoma of rectum	4	
Adenocarcinoma of colon	4	
Adenocarcinoma of jejunum	1	
Adenocarcinoma of uterus	1	
Adenocarcinoma of ovary	2	
Adenocarcinoma of breast	2	
Cylindroma of salivary gland	1	
Cylindroma of nasal fossa	1	
Mixed tumor of jaw	1	
Hypernephroma	3	
Squamous-cell epithelioma of skin	1	
Squamous-cell epithelioma of larynx	1	
Squamous-cell epithelioma of cervix	2	
Melanoma	3	
Hemangio-endothelioma	1	
Teratoma of testis	4	
Sarcoma		11
Fibrosarcoma	6	
Osteogenic sarcoma	3	
Giant-cell tumor of bone	1	
Ewing's tumor	1	

the tumors were classed as sarcomas. The commonest tumor was adenocarcinoma of the bowel, the primary lesion of which was located in the jejunum in one patient, in the colon in four patients, and in the rectum in four patients. Teratoma of the testis also occurred 4 times. Hypernephroma and melanoma were each encountered 3 times. There were two cases each of adenocarcinoma of the ovary, adenocarcinoma of the breast, and squamous-cell epithelioma of the cervix. Adenocarcinoma of the uterus, cylindroma of the salivary gland and of the nasal fossa, mixed tumor of the jaw, squamous-cell epithelioma of the skin, squamous-cell epithelioma of the larynx, and hemangioma were each encountered once. The commonest of the sarcomas was fibrosarcoma, which was found in six patients. Osteogenic sarcoma accounted for three cases and giant cell tumor and Ewing's tumor each for one.

Time Interval Between Removal of the Primary Tumor and Removal of the Pulmonary Metastatic Growth.—In two instances the pulmonary metastasis was removed before a primary growth was excised. The interval between the two procedures varied in the remaining patients from 2 to 270 months. The pulmonary resection was performed between 1 and 5 years following removal of the primary growth in twenty-five of the forty-three cases.

Type of Operation.—All forms of pulmonary resection were employed in this group of patients. Lobectomy was most frequently the procedure of choice, being utilized 26 times. Pneumonectomy was performed for twelve of the patients. Local excision, including wedge resection, was used 4 times (once as a second resection after lobectomy and a recurrence of the metastatic lesion), and segmental resection was used twice. There has been a trend toward more conservative resection of pulmonary tissue for metastatic tumors. Pneumonectomy was performed in 28 per cent of all cases in the series, but in only 15

per cent of the cases in which operation was performed during 1951. On the other hand, the local excisions and segmental resections were all carried out during 1950 and 1951.

Survival Periods.—The pertinent data for each case are summarized in Table III. One patient failed to reply to follow-up letters after leaving the Clinic. Another patient succumbed 1 month after pulmonary resection while still in the hospital and represented the only hospital death in the group. The survival statistics are based on the remaining forty-one patients who were successfully followed (Table IV).

The longest period of survival in the series was for more than 6 years in three cases. Two of these patients were still living 78 and 77 months after operation while the third had succumbed 81 months postoperatively.

Among the forty-one patients, thirty (73.2 per cent) survived for longer than 1 year. Twenty patients underwent operation at least 3 years prior to the close of this study, and two of these were not traced for as long as 3 years. Six (33.3 per cent) of the eighteen traced patients were living 3 or more years after operation. Eleven patients were followed for at least 5 years after operation; three of them (27.3 per cent) survived this interval.

The presence or absence of preoperative pulmonary symptoms had little, if any, prognostic bearing. Since most of the patients underwent operation in recent years, only 1-year survival rates will be calculated when comparing various factors. Of the total forty-one patients, twenty-three were asymptomatic, of whom seventeen (73.9 per cent) lived 1 year or more after operation. Among the eighteen patients with preoperative pulmonary symptoms, thirteen (72.2 per cent) lived 1 year or more. The mean interval between the operations for the removal of the primary and metastatic tumors was 36 months for the asymptomatic group and 59 months for the group with symptoms. Thus, the presence of pulmonary symptoms should not in itself deter the decision for resection of pulmonary metastasis.

In general, the larger lesions, as measured by roentgenographic means, were associated with shorter survival periods. The 1-year survival rate for the larger lesions was 50 per cent as compared with 75 per cent for the smaller lesions. Measurements were made on only sixteen patients, eight in each group. The patient with the largest metastatic lesion (7 cm. in diameter) died 10 months after operation. There were only two patients in the series whose tumors appeared multicentric on the roentgenograms. These died 6 and 10 months postoperatively.

Exfoliated malignant cells were found in the sputum in only three cases. In addition there were eight cases with negative results of sputa examinations. These groups are obviously too small to permit any conclusion regarding the prognostic significance of exfoliation of cells from the metastatic lesions.

A review of the bearing of the pathologic nature of the tumor on the survival period permits few if any unqualified conclusions. Among the eleven patients with sarcoma, six (54.5 per cent) lived 1 year or more after operation. Of the thirty patients with carcinoma, twenty-four (80.0 per cent) lived 1 year or more after operation. Thus, there is a somewhat more favorable outlook for patients with carcinoma than for those with sarcoma.

TABLE III. PULMONARY RESECTION FOR METASTATIC MALIGNANT LESIONS: DATA ON 43 CASES

CASE	PRIMARY LESION, TYPE AND SITE	TIME INTERVAL (MONTHS) FROM REMOVAL OF PRIMARY TUMOR TO PULMONARY RESECTION	OPERATION	MONTHS AFTER PULMONARY RESECTION		
				WITHOUT RECURRENCE	UNTIL RECURRENCE	UNTIL DEATH
1	Adenocarcinoma, rectum	48	Lobectomy		12*	
2	Adenocarcinoma, rectum	24	Lobectomy		12	16
3	Adenocarcinoma, rectum	12	Lobectomy			12
4	Adenocarcinoma, rectum	51	Lobectomy		8	12
5	Adenocarcinoma, colon	0	Pneumonectomy		20	24
6	Adenocarcinoma, colon	72	Lobectomy			12
7	Adenocarcinoma, colon	60	Lobectomy	40		
8	Adenocarcinoma, colon	36	Pneumonectomy			12
9	Adenocarcinoma, jejunum	0	Pneumonectomy			1
10	Adenocarcinoma, uterus	36	Lobectomy	No data		
11	Adenocarcinoma, ovary	180	Pneumonectomy	14		
12	Adenocarcinoma, ovary	48	Lobectomy	78		
13	Adenocarcinoma, breast	120	Lobectomy	45		
14	Adenocarcinoma, breast	48	Segmental resection	21		
15	Cylindroma, salivary gland	60	Lobectomy	20		
16	Cylindroma, nasal fossa	12	Lobectomy		12	19
17	Mixed tumor, jaw	270	Pneumonectomy		5	12
18	Hypernephroma	37	Pneumonectomy		66	81
19	Hypernephroma	48	Pneumonectomy	31		
20	Hypernephroma	2	Lobectomy			1
21	Squamous-cell epithelioma, thumb	48	Lobectomy	24		
22	Squamous-cell epithelioma, larynx	108	Lobectomy		5	21
23	Squamous-cell epithelioma, cervix	24	Lobectomy	25		
24	Squamous-cell epithelioma, cervix	48	Lobectomy	26		
25	Melanoma, right shoulder	36	Lobectomy			6
26	Melanoma, left shoulder	48	Segmental resection			7
27	Melanoma, left forearm	48	Lobectomy		3	4
28	Hemangio-endothelioma	120	Pneumonectomy			31
29	Teratoma, testis	12	Lobectomy			6
30	Teratoma, testis	36	Pneumonectomy		2	4
31	Teratoma, testis	15	Lobectomy		18	21
32	Teratoma, testis	12	Lobectomy	39		
33	Fibrosarcoma, right chest wall	6	Pneumonectomy			10
34	Fibrosarcoma, right leg	132 169†	Lobectomy Local excision	40	36	
35	Fibrosarcoma, back	48	Lobectomy			3
36	Fibrosarcoma, arm	2	Local excision			10
37	Fibrosarcoma, back	36	Lobectomy		9	12
38	Fibrosarcoma, elbow	144	Lobectomy		6	18
39	Osteogenic sarcoma, os calcis	60	Lobectomy		3	11
40	Osteogenic sarcoma, tibia	72	Pneumonectomy			15
41	Osteogenic sarcoma, scapula	48	Pneumonectomy	19		
42	Giant-cell tumor, tibia	18	Local excision	28		
43	Ewing's tumor, humerus	7	Local excision			8

*Living 23 months.

†Patient underwent second pulmonary resection for recurrence 37 months after first pulmonary resection. Free from further recurrence 40 months later, 77 months after first pulmonary resection.

The variation in survival period among patients with pathologically similar tumors was great. The shortest survival period of a patient with fibrosarcoma was 3 months; yet one was living without recurrence 77 months after operation.*

TABLE IV. SURVIVAL PERIODS* FOLLOWING PULMONARY RESECTION FOR A METASTATIC MALIGNANT LESION

SURVIVAL PERIOD, YEARS	CONDITION AS OF LAST REPORT	
	LIVING	DEAD
Less than 1	0	11
1, but less than 2	5	12
2, but less than 3	5	2
3, but less than 4	3	0
4, but less than 5	0	0
5, but less than 6	0	0
6, but less than 7	2	1

*Exclusive of one untraced patient and one patient who died in the immediate postoperative period.

Three of the six patients with fibrosarcoma lived for 1 year or more. One of the three patients with osteogenic sarcoma was living 19 months postoperatively, while the other two succumbed at 11 and 15 months. The patient with a giant-cell tumor was living 28 months after operation, while the child with Ewing's tumor had died in 8 months. All three patients with melanomas died in 7 months or less. The patient with hemangio-endothelioma survived for 31 months. Squamous-cell epithelioma carried a more favorable prognosis. With the exception of the patient whose lesion arose in the larynx, all were living at the completion of this review. The periods elapsed were 25 and 26 months for two patients with lesions of the cervix, and 24 months for the one with the thumb lesion. The patient with squamous-cell epithelioma of the larynx died 21 months after operation. Of the four patients with carcinoma of the rectum all had recurrences within a year and two had died within a year. The outlook for the four patients with carcinoma of the colon was somewhat more favorable. One was surviving 40 months after operation without evidence of recurrence. The others had died at intervals of 24, 12, and 12 months after removal of the metastatic growth. The patient with carcinoma of the jejunum died before the primary growth was removed. Both patients with carcinoma of the ovary survived, one being alive without recurrence 14 months, and the other, 78 months following operation. In two of the four cases of teratoma of the testis, the patients had died within 6 months. In contrast, another was living 39 months after operation. Two of the three patients with hypernephroma had favorable results. One lived 81 months after operation, while the other was free of apparent recurrence after 31 months. The third patient died 1 month after pulmonary resection. Of the two patients with cylindroma, the patient with the nasal-fossal lesion survived 19 months, while the one with the salivary-gland lesion was living 20 months following its removal. The patients with the mixed tumor of the

*This latter patient presented one of the most remarkable histories of the group. A woman, 20 years of age in 1946, at the time of her right lower lobectomy for metastatic fibrosarcoma, had previously, in 1935, and again, in 1939, had the primary and a recurrent lesion excised from the right leg. A local recurrence was again excised 1 month after pulmonary resection. In 1949, two nodules of metastatic tissue were removed by local excision from the right upper lobe. One month later the right leg was amputated through a level in the lower part of the femur for further recurrent local tumor. In March, 1953, she reported that she was in excellent health, had married, and had a child 9 months old.

jaw lived only 12 months. Both patients with adenocarcinoma of the breast were free of any evidence of recurrence 21 and 45 months after removal of the pulmonary metastatic lesion.

The interval between the removal of the primary and metastatic tumors appeared to influence the chances for survival; that is, the greater the interval, the better the survival. Of the seventeen patients whose metastatic tumors were removed during an interval of 3 years or less following excision of the primary growth, nine (52.9 per cent) lived 1 year or more following operation. Of the twenty-four patients whose metastatic tumors were removed more than 3 years after the primary operation, twenty-one (87.5 per cent) lived 1 year or more following operation.

The pulmonary resections consisted of pneumonectomies, lobectomies, and local excisions and segmental resections. Twelve patients were treated by pneumonectomy, and of these, one patient died in the hospital. Of the remaining eleven patients, nine (81.8 per cent) lived 1 year or more following operation. Lobectomy was performed 26 times. One patient was untraced. Among the twenty-five traced patients, nineteen (76.0 per cent) lived 1 year or more following operation. Local excisions and segmental resections were carried out on the remaining five patients (excluding the patient whose second pulmonary resection consisted of local excision). Three died within 12 months following thoracotomy, while the other two were without evidence of recurrence 21 and 28 months later.

COMMENT

The exact value of pulmonary resection for metastatic tumors remains difficult to assess solely on the basis of survival statistics. The degree of palliation afforded each of these patients likewise was not measurable. Few of these patients manifested truly disabling pulmonary symptoms. Doubtless, pulmonary resection spared many of them this dreaded terminal distress, while still others were relieved of the constant reminder of the presence of a malignant lesion in the guise of a persistent cough, hemoptysis, or chest pain. Criticism of the worth of the procedure should always be tempered by awareness of these often overlooked benefits of removal of the secondary tumor.

Facing the clinician and the surgeon contemplating exploratory thoracotomy in a patient who has previously been treated for malignant disease is the real possibility that the pulmonary lesion may be totally unrelated to the earlier disease. Regardless of one's opinion of the value of resection of metastatic tumors, there exists this disquieting possibility should the decision be made against operation. Further, the low mortality rate (2 per cent) for the patients in this series provides no support for avoiding exploration.

The number of patients followed for 3 and 5 years is yet too small to utilize these traditional survival figures in discussion of this procedure. The figures of 33 per cent and 27 per cent, respectively, for 3-year and 5-year survival periods in this study, while in themselves respectable values, are consequently of limited significance.

Criteria for judging the advisability of operation remain obscure. In general, the chances of "cure" are slightly greater for patients with small lesions

that have been discovered more than 3 years following removal of the primary growth than for other patients. No great difference was found in the survival among patients with carcinoma and sarcoma. Patients with melanoma, teratoma of the testis, and carcinoma of the rectum apparently received less benefit than certain others. In contrast, the outlook was relatively favorable for patients with squamous-cell carcinoma of the skin and cervix, adenocarcinoma of the colon, ovary, and breast, and hypernephroma. A decision based solely on the pathologic nature of the parent tumor, however, is fraught with considerable hazard because of the occasional "cure" obtained even with highly lethal tumors. Such a case is that of the patient with metastasis, secondary to a teratoma of the testis, who was alive without recurrence 39 months after its removal.

The extent of the pulmonary resection did not in itself appear to be a factor in the length of survival. Conservative resections may have more applicability for metastatic tumors than for bronchiogenic carcinoma, since the former are less likely to spread by lymphatic channels. In addition, choice of the less disabling procedure finds further support in the fact that the value of pulmonary resection for metastatic disease remains unestablished.

The results of this study would appear to justify the continuance of pulmonary resection for metastatic malignant lesions of the lungs. The palliation offered is noteworthy, and the prolongation of life is frequently gratifying.

REFERENCE

1. Seiler, H. H., Clagett, O. T., and McDonald, J. R.: Pulmonary Resection for Metastatic Malignant Lesions, J. THORACIC SURG. **19**: 655-675, 1950.

EXFOLIATIVE CYTOLOGY AND PULMONARY CANCER

A Histopathologic and Cytologic Correlation

Harlan J. Spjut, M.D.,* Dorothy J. Fier, B.S., and
Lauren V. Ackerman, M.D.
St. Louis, Mo.

THE value of cytology as an aid in the diagnosis and perhaps earlier detection of pulmonary cancer has been well established. The appearance, practical disappearance, and then reappearance of cytology as a diagnostic tool was brought out in the reviews of the history of cytology.[6, 14, 29] Numerous reports have appeared in the literature in the last decade, pointing out the degree of success and failure of sputum and bronchial washings. Success has varied. Iversen[15] and Liebow and co-workers[19] reported less than 50 per cent positive cytologic examinations in histologically proved lung cancers. In the intermediate group, 61 to 74 per cent positive smears has been reported.[4, 16, 22, 33] More enthusiastic reports[6, 23, 29] show between 80 to 90 per cent positive results. It should be pointed out that O'Keefe[23] concerned himself entirely with bronchial washings with 88.6 per cent positive smears in 307 proved pulmonary cancers.

That the examination of pulmonary secretions for cancer cells is valuable is not doubted. But, what are the limitations of this procedure? What information other than the report of positive, suspicious, or negative is gained by cytologic examinations? Segments of these two questions have been examined by several writers. The relationship between cytology and histologic type of lesion and between cytology and location of the lesion has been explored.[5, 15, 19, 20, 24, 25, 27] Correlation between resectability and cytology has been mentioned by different writers.[15, 16, 32] O'Keefe[23] makes an observation concerning cytology, bronchial biopsies, and cancer in pulmonary lymph nodes. With a positive cytologic report and a positive bronchial biopsy, the lymph nodes were positive in approximately 50 per cent of 21 cases. A negative bronchial biopsy and a positive cytologic examination yielded two out of eighteen cases with positive lymph nodes.

MATERIAL AND METHOD

In an attempt to evaluate the two questions, we have studied 501 histologically proved pulmonary cancers and their cytologic examinations. These cases were admitted to Barnes Hospital between July, 1948, and April 1, 1953. In each case at least one sputum or bronchial secretion was studied for neoplastic cells. There has been no selection of cases on the basis of an

From the Department of Surgical Pathology, Washington University School of Medicine and Barnes Hospital.
Received for publication Dec. 28, 1954.
*Fellow of the American Cancer Society.

optimum number of examinations. Our method of collection of sputa, preparation of smears, review of slides, and reporting of results has been previously outlined.[16]

For this study all of the positive smears and the suspicious smears in cases without a positive smear were reviewed. A representative smear from cases with negative cytology was reviewed. This was done by one of us (D. F.). The histologic typing of the smears was done (by D. F.) and checked (by H. J. S.). The typing was done without knowledge of the pathologic diagnosis. All of the histologic sections from each of the cases were reviewed by two of us (H. J. S. and L. V. A.). Our cases fell into the histologic cell type and sex grouping as generally reported in the literature[2, 8] (Table I). We vary slightly with other writers[5, 20, 24, 25] in that they had a greater number of undifferentiated carcinomas and fewer squamous-cell carcinomas than

TABLE I. HISTOLOGIC TYPE AND SEX DISTRIBUTION OF CASES

TYPE	TOTAL		MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Epidermoid carcinoma	269	53.7	252	94.6	17	6.4
Undifferentiated carcinoma	143	28.5	136	95.1	7	4.9
Adenocarcinoma	36	7.2	22	61.1	14	38.9
Bronchiolar carcinoma	4	0.8	2	50.0	2	50.0
Bronchial adenoma	11	2.2	7	63.6	4	36.4
Metastatic cancer	29	5.8	15	51.7	14	48.3
Others	9	1.8	7	77.7	2	22.3

did we. One notable deviation in our group was the 38.9 per cent occurrence of primary adenocarcinoma of the lung in the female. This figure is higher than usually reported.

Among the 501 cases, there were 318 bronchial biopsies, 95 other biopsies, 163 pneumonectomies, 35 lobectomies, 126 thoracotomies for exploration, and 35 autopsy examinations contributing to tissue confirmation of cancer. In each of the cases at least one sputum or bronchial washing was studied for cancer cells. Thus, there were 905 sputum examinations for 424 of the cases, and 364 bronchial washings for 343 cases. As would be expected, many cases had both types of examination. The total of cytologic studies in this series was 1,269. During the time period covered in this paper, there were 4,992 sputa and bronchial washings examined in the Barnes Hospital Cytology Laboratory. Including the positive smears used in this study, there were 483 positive sputa and bronchial washings among the 4,992 specimens. These were made up of 342 positive sputa and 141 positive bronchial washings. The positive reports represent 9.6 per cent of all examinations (approximately one in ten examinations). There have been no false-positives between May, 1951, and the preparation of this manuscript, May, 1954.

Breakdown of the cases in this series, as to their cytologic diagnosis, yielded 243 positive, 53 suspicious, and 205 negative cytologic examinations. On review of the suspicious and negative smears, 47 were changed to positive and 12 negative smears changed to suspicious. The cause for change in the diagnosis of the smears was the result of a combination of conservatism at the time of the original examination and was undoubtedly tempered by the

knowledge on the part of the reviewer that the case had proved to be cancer. Including the changes, there are 290, 28, and 183 cases with positive, suspicious, and negative cytologic examinations, respectively (Table II). Percentagewise, 57.8 per cent of the cases had a positive cytologic report, 5.7 per cent suspicious, and 36.5 per cent negative.

TABLE II. CYTOLOGIC DIAGNOSES IN 501 CASES OF HISTOLOGICALLY PROVED CARCINOMA

Cases cytologically positive		243
Cases cytologically suspicious		53
On review changed to positive	37	
On review remained suspicious	16	
Cases cytologically negative		205
On review changed to suspicious	12	
On review changed to positive	10	

Of the 318 bronchial biopsies, a diagnosis of cancer could not be made on 107 (33.7 per cent). A diagnosis of cancer was made on 211, or 66.3 per cent. These two groups were divided into operable and inoperable cases. Operable cases were considered as those in which a pneumonectomy or lobectomy was performed. It is readily apparent from study of Table III that inoperable cases yield a higher percentage of positive biopsies than do operable cases. Only *28.0 per cent* of the operable cases had a positive bronchial biopsy. An earlier report on a smaller number of cases from our hospital indicated 36 per cent positive bronchial biopsies in resectable cases. Approximately 59 per cent of pneumonectomies and lobectomies reported by Woolner and McDonald[32] in 1949 had positive bronchial biopsies. Our results for total positive biopsies compare closely with those of several other writers.[5, 20, 24, 31, 32] Their percentage of positive bronchial biopsies ranges from 63 per cent to 76 per cent. Below these figures are those of Herbut and Clerf[12] (42.1 per cent); O'Keefe, (33.8 per cent); and Gibbon and associates,[9] (24 per cent).

TABLE III. BIOPSIES AND THEIR RELATIONSHIP TO OPERABILITY

	BRONCHIAL BIOPSIES	OTHER BIOPSIES
Negative for cancer	107 (33.7%)	18 (19.0%)
Operable	47 (43.9%)	4 (22.3%)
Inoperable	60 (56.1%)	14 (77.7%)
Positive for cancer	211 (66.3%)	77 (81.0%)
Operable	59 (28.0%)	3 (3.7%)
Inoperable	151 (72.0%)	74 (96.3%)
Total	318	95

To obtain the 318 biopsies, 489 bronchoscopic examinations were performed in 459 of the cases. Forty-two of the patients were not examined bronchoscopically. No biopsy was taken in 171 of the bronchoscopic examinations. All but 29 had bronchial washings. The 171 were divided into groups: "normal bronchoscopic examination" and "deformity seen" (Table IV). The number of bronchial washings and sputa were tabulated under these headings. The percentage of positive sputa and bronchial washings for this group was below that for the entire series, from 0.0 to 5 per cent for sputa and 4 to 15 per cent for bronchial washings. This was particularly true when

compared with cytologic examinations accompanied by positive bronchial biopsies. This would be expected when the tumor was in reach. With a normal bronchoscopic examination there was a higher percentage (27.8 per cent) of positive bronchial washings than with observable deformity. In the latter group the percentage of positive bronchial washings is 16.2 per cent.

TABLE IV. CASES WITH NO BRONCHIAL BIOPSY

	SPUTA (TOTAL NUMBER, NOT CASES)				BRONCHIAL WASHINGS (TOTAL NUMBER = 1 PER CASE)			
	NEGATIVE	SUSPICIOUS	POSITIVE	NO SPECIMEN	NEGATIVE	SUSPICIOUS	POSITIVE	NO SPECIMEN
No bronchoscopic examination (42 cases)	63	3	21					42
Normal bronchoscopic examination (127 cases)	132	18	58 (27.8%)	29	70	7	27 (27.8%)	23
Deformity seen (44 cases)	55	5	17 (22.0%)	6	28	3	6 (16.2%)	7

Note: Only the percentage of positive cytologic diagnoses is computed. It is based on the number of examinations in each of the three categories. Sputum and bronchial washings are calculated separately.

Sputa were positive in 27.8 and 22.0 per cent, respectively. If the bronchi appeared normal to examination, the percentage of positive sputa was comparable to that of the entire group reviewed (501 cases). Sputa from those cases with no bronchoscopic examination were positive in 24.1 per cent. O'Keefe was able to diagnose 30.6, or 94 cases, with entirely normal bronchoscopic findings by means of bronchial aspirate. The number of aspirations per case is not given. Although we anticipated a higher percentage of positive cytologic examinations than was obtained in the group of "deformities," this was not the case. The deformities ranged from hyperemia to stenosis. We are unable to explain this finding unless compression of a bronchus prevents procurement of a satisfactory washing. *The fact that is important, however, is that, with no bronchial biopsy and a normal to near normal bronchial tree, one out of four cytologic examinations will be positive.*

Ninety-five "other" biopsies were obtained. These included aspiration biopsies of the lung, various lymph nodes, skin nodules, etc. Lymph nodes were the most commonly obtained specimen. Divided in a manner similar to the bronchial biopsies, there were 18 with no cancer diagnosis and 77 diagnoses of cancer. As would be expected, the number of inoperable cases was overwhelming, particularly in those with positive biopsies (Table III).

PRESENTATION OF DATA

In trying to answer in part the questions asked in the second paragraph we have made various correlations between the histologic, clinical, and cytologic aspects of our cases. The information derived will be developed in future sections of this paper. Some of the information seems valueless, whereas other observations serve to define the value and limitations of exfoliative cytology in pulmonary cancer.

Comparing the total number of bronchial washings and sputum examinations, it was noted that the percentage differences were not great. Among the 364 bronchial washings there were 59.3 per cent negative, 9.1 per cent suspicious, and 31.6 per cent positive examinations. The 905 sputa yielded 62.5 per cent negative, 10.4 per cent suspicious, and 27.1 per cent positive examinations. These figures give a slight advantage to bronchial washings in the way of a diagnosis of positive. Others[6, 16, 19, 32] have found the reverse to be true in their cases. Two observers[12, 13] found bronchial washings to be more reliable than sputum examinations. The obvious advantage of sputum for cell study is its availability and its repeated availability. This is particularly important considering the discomfort and apprehension associated with one and, more than one, bronchoscopic examination. Because of this and other factors an optimum number of specimens for a satisfactory examination has been cited by numerous observers. The figures usually range from 3 to 5. Philps[26] implies that five examinations would be optimum. In his 30 cases diagnosed cytologically, all of the diagnoses were made with five and less sputum specimens. Of 121 cases, Hjelt[14] diagnosed 112 with just two sputum samples. It seems that the optimum number of specimens varies a great deal. Our cases have been divided into three groups: less than three specimens, three specimens, and more than three specimens. These include sputa and bronchial secretions. It is noted that with three, and more than three studies, there is a distinct increase in the percentage of positive cases when compared to those with less than three examinations (Table V). This is particularly striking when there is no bronchial biopsy or a negative bronchial biopsy. In the presence of a positive bronchial biopsy the percentage difference of the groups is not great. The advantage of at least three cytologic examinations per case is evident. Our cases are most numerous in the first group (less than three specimens).

TABLE V. NUMBER OF SPECIMENS AND CYTOLOGY

	NO BRONCHIAL BIOPSY			NEGATIVE BRONCHIAL BIOPSY			POSITIVE BRONCHIAL BIOPSY		
	CASES AND PER CENT			CASES AND PER CENT			CASES AND PER CENT		
	NEGATIVE	SUSPICIOUS	POSITIVE	NEGATIVE	SUSPICIOUS	POSITIVE	NEGATIVE	SUSPICIOUS	POSITIVE
Less than 3 specimens/case	71	5	39	16	9	16	39	12	61
	61.5%	4.4%	33.9%	39.0%	22.0%	39.0%	34.8%	10.7%	54.5%
3 specimens/case	23	5	24	5	6	10	16	3	40
	44.2%	9.7%	46.1%	23.8%	28.6%	47.6%	27.0%	5.3%	67.7%
More than 3 specimens/case	17	4	22	8	3	13	10	6	18
	39.5%	9.3%	51.2%	33.3%	12.5%	54.2%	29.4%	17.7%	52.9%

Note: The percentage is calculated for each separate category. The diagnoses changed in the review for this study are not included in this table.

SITE AND SIZE OF THE LESION

The relationship between the cytology and the lung involved showed no startling differences except in bronchial washings from the right lung, in which 77, or 34.6 per cent, were positive. From the left lung there were 138 bronchial washings with 38 (27.5 per cent) positive. As to sputum studies,

362 specimens were from patients with cancer of the left lung and 535 from patients with cancer of the right lung. There were 103 (28.7 per cent) positive from the left lung and 139 (26.0 per cent) from the right lung. These figures were derived from 498 cases, as the location of the lesion could not be accurately determined in three cases. In an effort to determine which lobe yields the most and the least number of positive examinations, we used all means available, operative, autopsy, bronchoscopy, and x-ray reports to locate the lesion as to lobe involved. Main bronchus neoplasms and hilar lesions were assigned to the upper lobes. Among our 498 cases, we had 168 right upper lobe, 136 left upper lobe, 18 right middle lobe, 95 right lower lobe, and 59 left lower lobe lesions. The remaining 22 were multiple lesions and could not be assigned to a specific lobe. The distribution of lesions by lobes compares closely to that in the large series of lung cancers reported by Aufses.[2] Cytologic examinations broken down by lobes showed the following interesting observations. Except for the left upper and right middle lobes, the bronchial washings yielded a significantly higher percentage of positive results. For example, in the left lower lobe there were 26 (21.8 per cent) positive sputa as against 15 (40.5 per cent) positive bronchial washings. In the two excepted lobes the positive sputa exceeded positive bronchial washings. The left upper lobe gave the highest percentage of positive sputa (31.6 per cent) and the left lower lobe the lowest (21.8 per cent). The right lower lobe contributed the highest percentage of positive bronchial washings (40.8 per cent) and the left upper the lowest (23.4 per cent). In other words, the two upper lobes produced the highest percentage of positive sputa and the lower lobes the highest percentage of positive bronchial washings. Perhaps the better drainage of the upper lobes explains the success of sputa in these lobes. The more suitable anatomy of the lower lobes for aspiration possibly accounts for the greater number of positive bronchial washings from these lobes.

To pin-point further the relationship between cytologic studies and location of the lesions, the specific site was determined as accurately as possible. Only pneumonectomies, lobectomies, or autopsied cases were used. In many instances, descriptions were vague which probably accounts for our small number of main bronchus lesions. Two hundred twenty-six cases were included in this portion of the study. As had been stated, bronchial washings yielded a slightly higher, or nearly equivalent, percentage of positive diagnoses than did sputa. This is true with one exception. This exception is in single and multiple peripheral lesions, without demonstrable connection with bronchi. In thirteen peripheral lesions of the right lung there were no positive bronchial washings and 20.8 per cent positive sputa studies. The fourteen peripheral lesions of the left lung showed 2 (28.6 per cent) positive bronchial washings and 4 (13.3 per cent) positive sputa. The number of examinations in each of the lungs is few. However, it is gratifying to note that lesions of segmental bronchi and of peripheral areas do yield a respectable percentage of positive cytologic diagnoses (Table VI). Other writers[19, 27] have demonstrated success in detecting peripheral lesions by cytologic means. Their number of cases is small. Farber and associates[7] examined sputa and bronchial

TABLE VI. CYTOLOGY AND SPECIFIC SITE OF LESION

SPECIFIC SITE OF LESION	CASES	NUMBER OF SPUTA SPECIMENS			NUMBER OF BRONCHIAL WASHINGS		
		NEGATIVE	SUSPICIOUS	POSITIVE	NEGATIVE	SUSPICIOUS	POSITIVE
Left main bronchus	7	9	0	7	0	0	4
		56.2%		47.8%			100%
Left major bronchi	30	32	5	19	8	0	8
		57.0%	9.1%	33.9%	50.0%		50.0%
Left segmental bronchi	57	61	8	29	26	3	11
		62.1%	9.3%	28.6%	65.0%	7.5%	27.5%
Left peripheral lesions	14	23	3	4	5	0	2
		76.6%	10.1%	13.3%	71.4%		28.6%
Right main bronchus	3	0	3	4	2	0	2
			42.8%	57.2%	50.0%		50.0%
Right major bronchi	49	86	6	21	20	2	12
		75.4%	5.4%	19.2%	58.8%	5.9%	35.3%
Right segmental bronchi	53	57	6	31	22	3	13
		60.6%	6.5%	32.9%	57.8%	8.0%	34.2%
Right peripheral lesions	13	18	1	5	13	2	0
		75.0%	4.2%	20.8%	86.6%	13.4%	

Note: The percentage was computed from the number of specimens for each separate category and separately for sputum and bronchial washings.

washings from 60 peripheral lesions. There were 4 positive bronchial washings and 32 positive sputa. Jennings and Shaw[17] reported 42 peripheral tumors of which 27 (64.3 per cent) had positive sputa. The success of the procedure as an aid in the diagnosis of peripheral and segmental lesions is evident.

The cytologic studies as related to the size of the lesion proved to be interesting. The size was measured in 191 of our cases. Lesions measuring up to 2 cm. in diameter, those from 4 to 7 cm. in diameter, and multiple lesions yielded fairly low percentages of positive cytologic studies. The percentage of positives ranged between 10 and 25 per cent. Those lesions which measured 2 to 3 cm. and over 7 cm. showed a definite percentage increase of positive studies. In the 2 to 3 cm. group there were 31.5 per cent positive sputa and 30.7 per cent positive bronchial washings. In the lesions over 7 cm., 35.8 per cent had positive sputa, and 37.5 per cent had positive bronchial washings. It appears that small lesions (2 cm. and less), middle-sized lesions, and multiple lesions do not readily give up their neoplastic cells. In their analysis of factors responsible for cytologic failures, Buffmire and McDonald[4] did not mention the size of the lesion. The significance of these findings is not readily apparent. We suspect that they mean nothing. However, it is possible to state that small lesions, less than 2 cm., do yield neoplastic cells even though the percentage is small. Thus, the examination may be said to be of some aid in defining the nature of small pulmonary lesions. Experiments by Appel and Bronk[1] support these observations. They transplanted tumor to bronchi of rabbits and made frequent periodic smears of the bronchi. In seventeen (58 per cent) of their animals tumor was recognized in the smear before it was evident grossly or by x-ray.

From our resections and autopsies, 134 cases were found to have positive regional lymph nodes. Ninety-four cases had negative nodes. With positive

nodes, bronchial washings yielded 35 (36.8 per cent) positive smears and with negative nodes 16 (24.6 per cent) positive smears. The percentage of positive sputa was nearly equal, 68 (27.0 per cent) with positive nodes, and 54 (30.3 per cent) with negative nodes. This is an observation the significance of which is not apparent.

Cytologic examinations in the 163 pneumonectomy cases totaled 307 sputa and 120 bronchial washings. Divided among the lobes, the bronchial washings were generally more rewarding in percentage of positive results than were sputa. The one exception was again noted to be in the left upper lobe. The right lower and left upper lobes showed the highest percentage of positive sputa, 33.3 per cent and 31.6 per cent, respectively. The lower lobes gave the highest percentage of positive bronchial washings, 39.1 per cent from the right lobe and 58.8 per cent from the left lobe. Thirty-five lobectomy cases produced 67 sputa and 26 bronchial washings. The numbers are few but show that sputa were more frequently positive in cases of cancer of the right lung. The number of positive bronchial washings and sputa was nearly equal in left lung lesions. In the 126 cases in which only an exploratory thoracotomy was done, 236 sputa and 92 bronchial washings were obtained. Bronchial washings showed a higher percentage of positive results in each lobe except the left upper, where there were 26 per cent positive sputa and 12.5 per cent positive bronchial washings. The cytologic examinations from the autopsied cases were so few as to make the results meaningless. The results, especially from the pneumonectomies, were similar to those in a preceding paragraph. Lobectomy and explored cases deviated slightly. We are unable to add any further explanation for these observations other than that mentioned.

Our number and grouping of bronchial biopsies have been mentioned on preceding pages. Cytologic studies associated with bronchial biopsies were interesting but fall into an expected pattern. There was a high percentage of positive bronchial washings (42.9 per cent) with positive bronchial biopsies. This result could well be altered by the technique of washing, that is, the vigor of the washing or whether it was done before or after the biopsy. If done after, it is conceivable that dislodged tumor cells may help make the cytologic examination successful. On the other hand, blood may obscure or dilute tumor cells so as to make their detection more difficult. Herbut[10] feels the amount of saline used is important; the return should be sticky. He found that with watery washings the results are uniformly poor. With a positive bronchial biopsy, sputa were positive 29.5 per cent of the time in our cases. With a negative bronchial biopsy or no bronchial biopsy, the percentage of positive sputa and bronchial washings was similar, ranging between 22.6 per cent and 26.1 per cent (Table VII). Thus, it would appear that as a pulmonary cancer becomes available to the biopsy forceps, the number of positive smears increases notably as would be expected. This is particularly true of bronchial washings.

With regard to operability and inoperability, the following observations were made. One hundred ninety-eight (39.5 per cent) cases were counted as

TABLE VII. CYTOLOGY AND BRONCHIAL BIOPSY

	SPECIMENS	PER CENT OF TOTAL	NO BRONCHIAL BIOPSY		NEGATIVE BRONCHIAL BIOPSY		POSITIVE BRONCHIAL BIOPSY	
			CASES	SPECIMENS	CASES	SPECIMENS	CASES	SPECIMENS
Negative BW*	216	(59.3%)	98	103 (70.0%)	40	43 (62.3%)	62	70 (46.9%)
Suspicious BW	33	(9.1%)	10	10 (7.4%)	8	8 (11.6%)	15	15 (10.2%)
Positive BW	115	(31.6%)	33	33 (22.6%)	18	18 (26.1%)	62	64 (42.9%)
No BW	158			72		19		67
Negative sputa	566	(62.5%)	128	250 (67.4%)	55	99 (63.0%)	114	217 (57.5%)
Suspicious sputa	94	(10.4%)	22	26 (7.0%)	19	21 (13.5%)	44	47 (13.0%)
Positive sputa	245	(27.1%)	68	95 (25.6%)	26	37 (23.5%)	83	113 (29.5%)
No sputa	77			37		12		28

*BW = Bronchial washing.

operable and 303 as inoperable. Gibbon[9] had 39 per cent resectable cases out of 484 pulmonary cancers, and Aufses[2] reported 17 per cent in over 900 pulmonary cancers. A small number of lobectomies and segmental resections were done for metastatic lesions in our series. In our group 110 (56.1 per cent) operable cases had positive cytology. Of the inoperable cases 179 (59.0 per cent) had positive cytologic examinations. With a positive biopsy as an added factor the results were very different. In our 252 cases in this group, 71.5 per cent were inoperable, and 22.3 per cent operable. These patients had a positive biopsy and a negative, suspicious, or positive cytology. When a negative biopsy was obtained or no biopsy taken, the percentage of operable cases is notably better. A positive cytology in the latter two groups does not influence the operability (Table VIII). It would appear from these observations that a positive cytologic examination does not influence the chance that a given case or group of cases will be operable or inoperable to the extent that a positive biopsy does. A positive biopsy, as far as our figures are concerned, means there is a 3 to 1 chance the case is inoperable.

The biopsies in the operable cases were all bronchial except six. Only one of the six was positive, an aspiration biopsy of the lung. Cytology is of no help to the clinician in the group of operable cases with positive biopsies;

TABLE VIII. OPERABLE AND INOPERABLE CASES

CYTOLOGY	BIOPSY	OPERABLE		INOPERABLE	
		CASES	PER CENT	CASES	PER CENT
Positive	Positive	39	14.5	123	45.8
Suspicious	Positive	9		2	0.7
Negative	Positive	21	7.8	67	25.0
Total		60	22.3	192	71.5
Positive	Negative	27	35.5	21	27.6
Suspicious	Negative	1	1.4	2	2.8
Negative	Negative	13	17.1	12	15.6
Total		41	54.0	35	46.0
Positive	No biopsy	43	27.3	30	19.1
Suspicious	No biopsy	3	1.8	1	0.6
Negative	No biopsy	39	24.8	32	20.4
Total		85	53.9	63	40.1

Note: In the total of operable and inoperable cases, there are 12 palliative resections (for metastases) and 13 cases who refused operation or were considered poor risks. Their totals were used in computing the percentages but are not shown on the chart.

it is only interesting. The cases in which the cytology is of greatest help are in those patients with positive cytology and either a negative or no bronchial biopsy. Fifty-nine cases fall into this group. These cases do not include those changed from negative or suspicious to positive when this study was undertaken (Table IX). In these cases, the cytology represented the sole positive tissue diagnosis prior to operation. The degree of trust placed in the cytologic diagnosis was indicated by the small number of frozen sections asked for by the thoracic surgeons. But 13 frozen sections were requested to confirm the diagnosis in our 59 cases. We feel that with a positive cytologic diagnosis the surgeon should go ahead with the resection without use of frozen section. By doing so, tumor tissue is not incised and thereby exposed to the pleura and other tissues. The possibility of implantation of cancer cells is minimized.

TABLE IX. CYTOLOGY AND BIOPSY IN OPERABLE CASES

	POSITIVE CYTOLOGY	NEGATIVE OR SUSPICIOUS CYTOLOGY
Positive bronchial biopsy	35 (17.7%)	25 (12.6%)
Negative bronchial biopsy	18 (9.1%)	20 (10.1%)
No bronchial biopsy	41 (20.3%)	59 (30.2%)

Note: The percentages are computed for the entire group. The cytology is reported as a case.

Thus, of the operable cases 29.8 per cent fell into the group in which a definitive diagnosis of cancer was made by the cytologic smear. Many other writers have had similar cases in their series. Watson and associates[30] reported 7 of 26 pulmonary resections, and Jennings and Shaw[17] 64, done on the basis of cytology alone. Woolner and McDonald[32] had 23 such patients in their group. Wandall's[29] 100 cases included 12 operated on with only a positive cytologic diagnosis. Of our 59 cases, 48 were resections with the cytology as the only positive preoperative tissue diagnosis, as only 13 frozen sections were requested, and 2 of these were reported as showing chronic inflammation. Resection was done in these two cases. It is in this group of patients that cytology is most helpful and represents the area in which every effort should be made to improve the accuracy of diagnosis.

TYPING OF SMEARS

A facet of pulmonary exfoliative cytology recently explored by Foot[8] is an interesting one, namely, the study of cytologic typing of the positive smears. In his review of 341 cases the over-all accuracy of typing is 80 per cent. The accuracy varied with the histologic type. His epidermoid carcinomas were accurately typed in 89.9 per cent of instances, whereas pleomorphic carcinomas were diagnosed in 69.2 per cent of the cases. Of 2 bronchial adenomas and 5 alveolar-cell carcinomas, none was correctly typed from the smears. Umiker[27] mentions that in his 14 cases with positive cytology a correct histologic typing was made in eleven. He states further, that in every instance epidermoid carcinoma and pleomorphic carcinoma were recognized.

In this study, cancer of the lung has been divided into seven groups: epidermoid carcinoma, undifferentiated carcinoma, adenocarcinoma, adenocarcinoma grade I (so-called bronchial adenoma), bronchiolar carcinoma, metastatic carcinoma, and others. The large-cell and small-cell carcinomas are included in our undifferentiated carcinomas. Included in our "other" tumors is one lymphosarcoma, a carcinosarcoma, and neoplasms which we were unable to classify. With these as our histologic groups we attempted to determine the types of our 290 cases with positive smears.

No appreciable difference in determining the histologic type was encountered between sputa and bronchial smears. Our criteria for typing the smear were similar to those of Foot and the Vincent Memorial Hospital group.[28] Because of the difficulty in distinguishing poorly differentiated epidermoid carcinomas and undifferentiated carcinomas, even histologically, a slight modification was made in our tabulations. If a cancer were found to be a poorly differentiated epidermoid carcinoma, histologically, and typed as undifferentiated, it was not counted as an error. The reverse of this was not used in tabulation.

Generally our typing (Table X) was as successful as Foot's and that of Memorial Hospital group used by Foot for comparison. We have an over-all accuracy of 79.3 per cent as determined from 230 correct and 60 incorrect. One case was not typed because of loss of the slides, but was counted as incorrect.

TABLE X. RESULTS OF CYTOLOGIC TYPING

	CYTOLOGIC TYPE AS DETERMINED FROM THE SMEAR (CASES)					
HISTOLOGIC TYPE	EPIDERMOID CARCINOMA	UNDIFFERENTIATED CARCINOMA	ADENOCARCINOMA	ALVEOLAR-CELL CARCINOMA	NEGATIVE AND SUSPICIOUS CYTOLOGY	TYPING ACCURACY
1. Well-differentiated epidermoid carcinoma	97	11	2	0	30	89.2%
2. Poorly differentiated epidermoid carcinoma	37	31	7	0	54	
3. Undifferentiated carcinoma	13	48	2	0	80	76.2%
4. Adenocarcinoma (includes metastatic adenocarcinoma)	4	13	11	0	32	39.3%
5. Bronchial adenoma	1	1	1	0	8	33.3%
6. Bronchiolar carcinoma	0	0	0	2	2	100%
7. Others	1	3	0	0	5	0.0%
8. Metastatic carcinoma (except adenocarcinoma)	3	0	0	0	2	100%

Note: Over-all typing accuracy was 79.3 per cent.

One hundred eighty-five cases of epidermoid carcinoma had positive smears. One hundred sixty-five were correctly typed for a percentage of 89.2 per cent. This compares with New York Hospital's 87.7 per cent. Our errors in this group were greatest in calling well-differentiated epidermoid carcinoma, undifferentiated. Nine were typed as adenocarcinoma. The undifferentiated carcinomas were typed accurately in 76.2 per cent of cases. Adenocarcinomas were typed correctly in 39.3 per cent of the cases. Included in adenocarcinomas are the bronchial adenomas and metastatic adenocarcinomas. Nine of our cases of metastatic carcinoma had positive cytologic

examinations. Most of the errors were in typing adenocarcinomas as epidermoid carcinomas. We were unable to differentiate primary and metastatic adenocarcinomas. Three metastatic epidermoid carcinomas were typed correctly. Of our 11 bronchial adenomas, 3 had positive smears. One was typed as undifferentiated carcinoma, one epidermoid, and one adenocarcinoma. The latter was considered correct because of our feeling that bronchial adenomas are adenocarcinomas, grade I. To illustrate further the difficulty of typing bronchial adenomas, Foot typed 2 in his series as anaplastic carcinomas. Two bronchiolar carcinomas of 4 in our group had positive smears. Both were typed correctly.

We feel that most of our errors may be explained by the vagaries of pulmonary cancers as far as their histology is concerned. Several of our cases show a combination of structure, e.g., epidermoid carcinoma with areas of adenocarcinoma. A few of the epidermoid carcinomas had areas which could readily be mistaken for a renal-cell carcinoma. Undifferentiated or poorly differentiated epidermoid carcinomas with large vacuolated cells could be confused with adenocarcinomas as far as the smear is concerned. It is difficult to explain the poor showing with adenocarcinomas. Several, histologically, were composed of cells with dense acidophilic, rather than vacuolated, cytoplasm, or were not well differentiated (Figs. 1 through 8).

Typing of smears may give the surgeon valuable preoperative information. The difference in prognosis between epidermoid and undifferentiated carcinoma is well known. This information and the implications as to resectability may be provided by the smear. Support for this is given by Borrie.[3] In a review of 200 resected pulmonary cancers he observed that 42.5 per cent of epidermoid carcinomas and 70 per cent of undifferentiated carcinomas had lymph node metastases. In cases of bronchiolar carcinoma, typing of smears gives information important to surgical treatment of the disease. It may aid in the decision as to lobectomy or pneumonectomy. To support this, Kirklin and McDonald[18] reported finding malignant cells in the sputa and bronchial washings of 9 out of 14 alveolar-cell tumors of the lung. Only one was diagnosed by biopsy. Typing of smears may well have its place on the report to the clinician.

DURATION OF SYMPTOMS

As a last bit of information which came to light in our study, we have the relationship between the duration of symptoms and the cytologic examinations. To date the duration of symptoms, we used the first complaint which seemed related to the illness that was made by the patient. We realize that the date of onset will vary with the manner in which and the persistence with which questions are asked of the patient. With that in mind, we have made the following observations. There were two peaks for bronchial washings and one for sputa, i.e., peaks for a high percentage of positive smears. The first for bronchial washings came at 3 months. The second, which is also the peak for sputa, came in the 6 to 11 months' period. In this latter time period, the sputa were positive in 34.7 per cent of examinations and bronchial washings in 36.0 per cent. Except for the peaks mentioned, the percentage of

Fig. 1. Fig. 2.

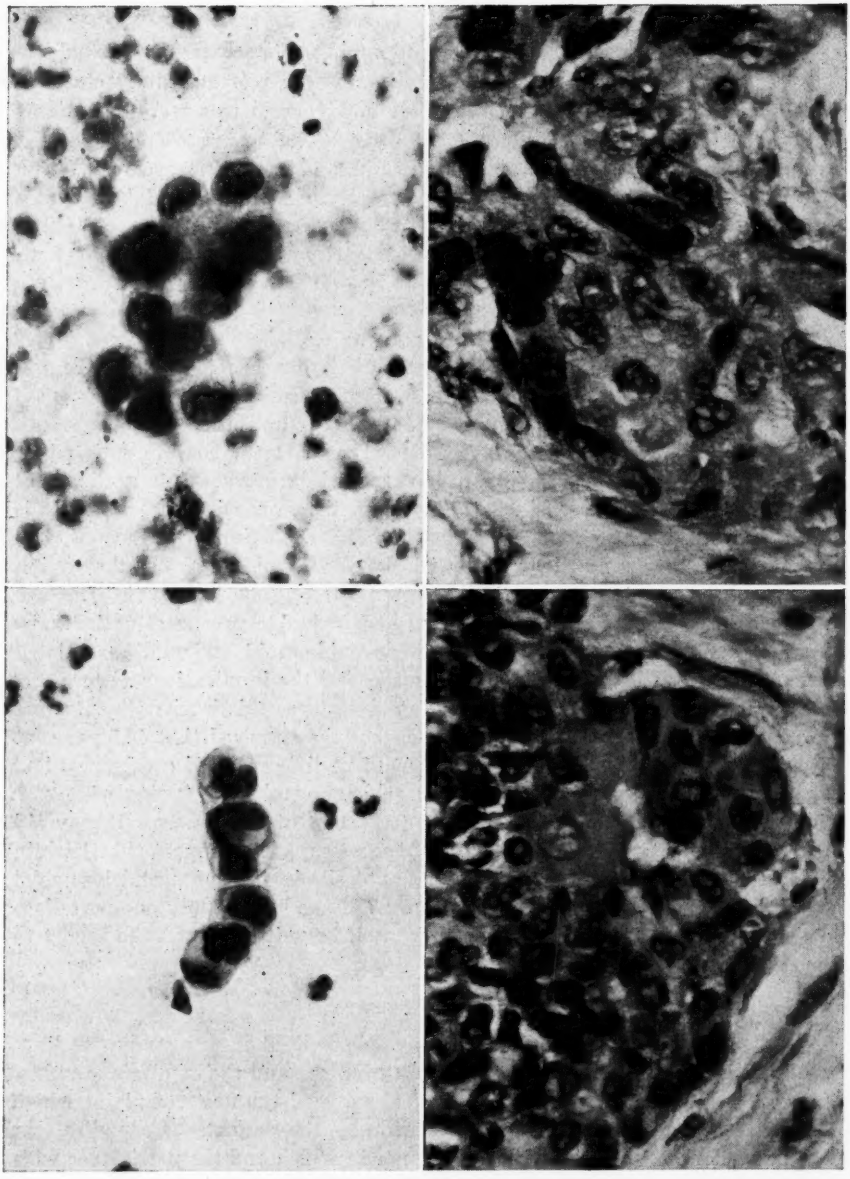


Fig. 3. Fig. 4.

Fig. 1.—Sputum was cytologically typed as adenocarcinoma because of vacuolation and was found to be histologically undifferentiated carcinoma. (×600.)

Fig. 2.—Tissue section is illustrative of an area in which the cells are similar to those in the sputum. (×600.)

Fig. 3.—Sputum was cytologically typed as adenocarcinoma because of apparent cytoplasmic vacuolation and was found to be histologically epidermoid carcinoma. (×600.)

Fig. 4.—Demonstrates an area of vacuolated cells in the tissue section which if exfoliated could be confused with adenocarcinoma. (×600.)

The illustrations of the tissue sections were taken at the same magnification as the smears to show cell detail and not histologic pattern in the case of the tissues.

Fig. 5. Fig. 6.

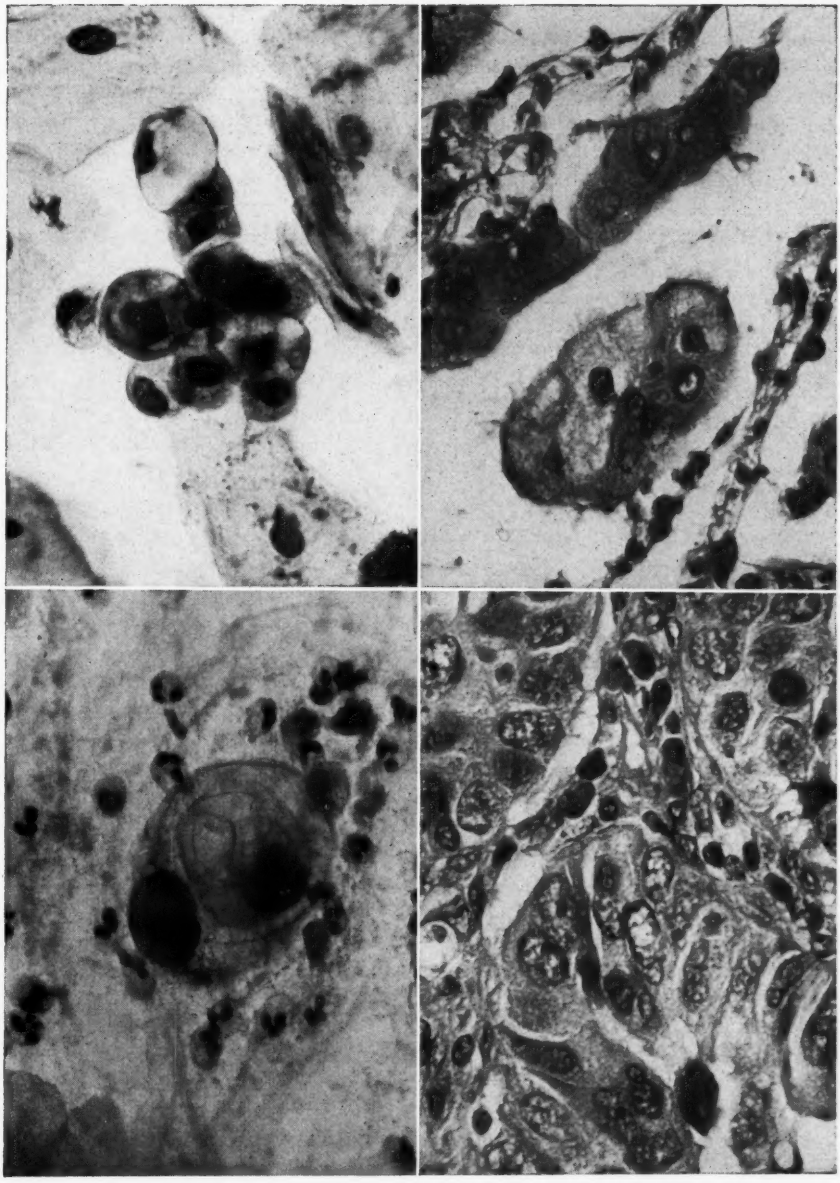


Fig. 7. Fig. 8.

Fig. 5.—Demonstrates an alveolar-cell carcinoma which was accurately typed cytologically. (×600.)

Fig. 6.—From a tissue section illustrating the similarity of the cells to those in Fig. 5. (×600.)

Figs. 7 and 8.—These two sections are sputum and tissue, respectively. This is an accurately typed adenocarcinoma, primary in the lung. (×600.)

The illustrations of the tissue sections were taken at the same magnification as the smears to show cell detail and not histologic pattern in the case of the tissues.

positive smears remains level in both sputa and bronchial washings. The most notable dip is to 20.7 per cent positive sputum examinations when the symptoms were present for one year or longer. From these observations, it might be stated that with manifest symptoms of short duration, up to 3 months, cytologic examinations are a distinct aid in diagnosis. Why there should be a difference in yield of positive examinations at different time periods we cannot say.

DISCUSSION

Our over-all success in positive cytologic diagnosis is 57.8 per cent. This is without correction for the so-called optimum number of examinations. If this correction is made, the number of cases with positive smears may potentially be as high as 85 to 90 per cent.[7, 16, 25] Our percentage for the optimum number of examinations is 76.6 per cent. The percentage was derived by eliminating cases with less than three cytologic examinations. This figure, or even those without correction, plus the fact that the number of false-positive examinations is almost at an irreducible minnimum, serves to emphasize the value and reliability of cytology as an indispensable aid in the workup of patients suspected of pulmonary cancer. Recently, McDonald[21] stated that in 1,500 positive reports at the Mayo Clinic there were 24 false-positive reports, or 1.6 per cent. At Barnes Hospital, as previously stated, there have been no false-positive reports during the past three years. Although the percentage of false-positives is low, the fact remains that it is the case which is important. Even one or two false-positives are too many when a needless pneumonectomy may have resulted because of the erroneous cytologic report. As a further step, it is suggested that cytologic examinations be used in the follow-up of patients with pulmonary resection. This would be of particular importance in bronchiolar carcinomas, with their known multiple foci. This phase of cytology has not been extensively explored by us, although cases of cancer persistent at the bronchial stump have been detected. One case of recurrent bronchiolar carcinoma has been diagnosed by follow-up cytology.

Bronchial washings throughout our study, with certain exceptions, were consistently more productive of positive results than were sputa. More than twice as many sputa were examined. This may account for the slightly lower percentage of positive smears. But the large numbers of both should be a point against the bronchial washings being superior to sputum examinations only on the basis of numbers. The consistency with which bronchial washings remain superior to sputum examinations when correlated with the site of the lesion, size, and duration would make it appear that for this series at least the observation seems valid. Both have their advantages, however. Sputum is readily available, repeatedly available, and inexpensive to procure. Bronchial washings have the advantage of being a more selective specimen as far as location of the lesion in the lung is concerned. They eliminate desquamated cells from other parts of the respiratory tract and mouth. In addition, bronchial washings are important in cases presenting with a nonproductive cough.

From the outset it was the purpose of this study to define the limitations of cytology in pulmonary cancer and perhaps to increase the information gained therefrom. Cytology is obviously of little value in the localization of a cancer in the respiratory system. In our review in regard to this point the right lung lesion gave a higher percentage of positive results than did the left. This was true of bronchial washings and sputum examinations. Both lower lobes yielded a fairly high percentage of positive bronchial washings compared to the other lobes. The sputa, on the other hand, were reasonably evenly distributed among the lobes. In our experience, cytologic findings are of no aid in localizing a lesion to a specific portion of a lobe. The only pertinent observation to be made is that the peripheral lesions arising in bronchioles give a low percentage of positive sputa and bronchial washings.

The size of the lesion, when correlated to the cytologic findings, showed the large tumors (above 7 cm.) and tumors 2 to 3 cm. give a significantly higher percentage of positive reports than did other lesions. With large lesions, this may be explained on erosion into multiple bronchi and bronchioles, thus greatly increasing the surface of tumor from which cells exfoliate. On the other hand, many large tumors display extensive necrosis. With large amounts of necrotic material in the secretions, results were supposedly poorer.[16] We have no explanation for the results obtained in the small neoplasms.

With erosion of the tumor or invasion of a bronchial wall as seen grossly or microscopically, more positive results occurred. In our 172 cases in which erosion or invasion was demonstrated 95 (29.5 per cent) of the sputa and 45 (36.3 per cent) of the bronchial washings were positive. Without erosion or invasion (56 cases) there were 27 (24.3 per cent) positive sputa and 6 (15.0 per cent) positive bronchial washings. These results are what one would expect. The number of tumors with erosion or invasion could undoubtedly be altered by taking more than the three sections of the tumor as we routinely do in our laboratory. Positive regional lymph nodes are associated with a higher percentage of positive cytologic (bronchial washings) results. The large majority of the nodes were dissected from surgically resected specimens. This latter finding suggested, even though weakly, that a positive bronchial washing may be a sign of poor prognosis. Interestingly enough, the duration of symptoms caused no great variation in the cytologic results. Notable is the low percentage of positive sputa in cases with symptoms of long duration. This may be a reflection of the slow progression of the tumor or that the lesion is more peripheral. Even with symptoms of short time span, a significant number of positive sputa and bronchial washings were obtained. This observation serves to emphasize the value of a cytologic examination in the face of unexplained respiratory symptoms even of short duration.

A comparison of operability versus inoperability is detailed in the body of this paper. Comparing lobectomies and pneumonectomies to cases only explored, we found the percentage of positive sputa and bronchial washings to be much the same in the two groups. This was not computed on a case basis. The findings are similar to those reported by Wandall.[29] Jennings and Shaw[17] feel that malignant cells in the sputum are found with equal frequency in operable or advanced cases. Iversen[15] had 47 per cent positive cytology in

inoperable cases as against 42 per cent in resectable cases. From our study it would seem that a positive biopsy in a given case means a greatly lessened chance for operability. A positive or negative cytology report does not seem to alter the chance of operability greatly. This is borne out by the number of cases with negative sputum and either a negative biopsy or no biopsy. In the operable group there were 52 such cases and 44 in the inoperable. It appears that cytology in pulmonary cancer is of little or no prognostic value.

SUMMARY

1. Five hundred and one histologically confirmed cases of pulmonary cancer and their cytology were reviewed.

2. For tissue confirmation there were 318 bronchial biopsies, 95 other biopsies, 163 pneumonectomies, 35 lobectomies, 126 exploratory thoracotomies, and 35 autopsies.

3. Twelve hundred sixty-nine cytologic smears were studied, including 905 sputa and 364 bronchial washings.

4. Thirty-one and six-tenths per cent of the bronchial washings were positive, and 27.1 per cent of the sputa were positive.

5. On a case basis the over-all percentage of positive reports was 57.8 per cent and with an optimum number (3 or more) specimens, 76.6 per cent.

6. The optimum number of sputa and bronchial washings for study was found to be three.

7. Of the 318 bronchial biopsies 211 or 66.3 per cent were positive. Only 28 per cent of the positive biopsies were in the operable cases.

8. The lower lobes yielded the highest percentage of positive smears (bronchial washings). The highest percentage of positive sputa was obtained from the left upper lobe.

9. Cytologic examinations are of value in the diagnosis of peripheral pulmonary cancers.

10. Lesions 2 to 3 cm. in diameter and those larger than 7 cm. produced the highest percentage of positive smears.

11. Cases with positive hilar and bronchopulmonary nodes yielded a higher percentage of positive bronchial washings than did those with negative nodes. Sputum examinations remained much the same for the two groups.

12. Positive smears were obtained in 56.1 per cent of the operable cases and 59 per cent of the inoperable cases.

13. With a positive biopsy, the number of operable cases decreases notably.

14. In 59 of our operable cases, the cytology was the only positive tissue examination prior to operation. Thirteen frozen sections (with eleven positive) were asked for in these cases. Thus, 48 of our cases were resected with cytology as the sole tissue diagnosis.

15. Typing of the positive smears was 79.3 per cent accurate. Epidermoid carcinomas were correctly typed in 89.2 per cent of instances, undifferentiated carcinomas in 76.2 per cent, and adenocarcinomas in 39.3 per cent. Two bronchiolar carcinomas were accurately typed from the smears.

We wish to acknowledge the valuable assistance of Mrs. Delores Wallen of the cytology laboratory.

REFERENCES

1. Appel, M., and Bronk, T. T.: Tumor Cells in Bronchial Secretions, Am. J. Clin. Path. **19**: 320-322, 1949.
2. Aufses, A. H.: Primary Carcinoma of the Lung, J. Mt. Sinai Hosp. **20**: 212-227, 1953.
3. Borrie, J.: The Surgical Pathology of Carcinoma of the Lung, Australian & New Zealand J. Surg. **23**: 55-62, 1953.
4. Buffmire, D. K., and McDonald, J. R.: Factors Responsible for the Failure of Cytologic Examination in Cases of Bronchiogenic Carcinoma, S. Clin. North America **31**: 1191-1197, 1951.
5. Carlisle, J. C., McDonald, J. R., and Stuart, W. H.: Bronchiogenic Squamous Cell Carcinoma, J. THORACIC SURG. **22**: 74-82, 1951.
6. Farber, S. M., Benioff, M. A., Frost, J. K., Rosenthal, M., and Tobias, G.: Cytologic Studies of Sputum and Bronchial Secretions in Primary Carcinoma of the Lung, Dis. Chest **14**: 633-664, 1948.
7. Farber, S. M., McGrath, A. K., Benioff, M. A., and Espen, L. W.: The Early Diagnosis of Primary Lung Cancer by Cytologic Methods, Dis. Chest **20**: 237-256, 1951.
8. Foot, N. C.: The Identification of Types of Pulmonary Cancer in Cytologic Smears, Am. J. Path. **28**: 963-983, 1952.
9. Gibbon, J. H., Allbritten, F. F., Templeton, J. Y., and Nealon, T. F.: Cancer of the Lung—An Analysis of 532 Consecutive Cases, Ann. Surg. **138**: 489-501, 1953.
10. Herbut, P. A., quoted from Bovd, W.: Symposium on the Cytologic Diagnosis of Cancer Am. J. Clin. Path. **19**: 341-346, 1949.
11. Herbut, P. A., and Clerf, L. H.: Cancer Cells in Bronchial Secretions, M. Clin. North America **30**: 1384-1392, 1946.
12. Herbut, P. A., and Clerf, L. H.: Bronchiogenic Carcinoma Diagnosis by Cytologic Study of Bronchoscopically Removed Secretions, J. A. M. A. **130**: 1006-1012, 1946.
13. Hjelt, L.: A Cytologic Diagnosis of Pulmonary Cancer, Acta path. et microbiol. scand. supp. **93**: 128-134, 1952.
14. Hjelt, L.: Cytologic Diagnosis in Pulmonary Cancer, Ann. chir. et gynaec Fenniae, suppl. **3**: 1-68, 1953.
15. Iversen, A. F.: Cytologisk lungediagnostic, Nord. med. **49**: 676-678, 1953.
16. Jackson, E., Bertoli, F., and Ackerman, L. V.: Exfoliative Cytology, J. THORACIC SURG. **21**: 7-23, 1951.
17. Jennings, R. C., and Shaw, K. M.: The Value of Cytological Examination of the Sputum in the Diagnosis of Carcinoma of the Bronchus, Thorax **8**: 288-294, 1953.
18. Kirklin, J. W., and McDonald, J. R.: Alveolar Cell Tumor of the Lung, M. Clin. North America **38**: 1139-1142, 1954.
19. Liebow, A. A., Lindskog, G. E., and Bloomer, W. E.: Cytologic Studies of Sputum and Bronchial Secretions in the Diagnosis of Cancer of the Lung, Cancer **1**: 223-233, 1948.
20. McBurney, R. P., McDonald, J. R., and Clagett, O. T.: Bronchiogenic Small Cell Carcinoma, J. THORACIC SURG. **22**: 63-73, 1951.
21. McDonald, J. R.: Exfoliative Cytology in Genitourinary and Pulmonary Diseases, Am. J. Clin. Path. **24**: 684-687, 1954.
22. McKay, D. G., Ware, P. F., Atwood, D. A., and Harken, D. E.: The Diagnosis of Bronchiogenic Carcinoma by Smears of Bronchoscopic Aspirations, Cancer **1**: 208-222, 1948.
23. O'Keefe, J. J.: The Cytologic Diagnosis of Primary Bronchiogenic Carcinoma, Laryngoscope **60**: 931-938, 1950.
24. Patton, M. M., McDonald, J. R., and Moersch, H. J.: Bronchiogenic Adenocarcinoma, J. THORACIC SURG. **22**: 83-87, 1951.
25. Patton, M. M., McDonald, J. R., and Moersch, H. J.: Bronchiogenic Large Cell Carcinoma, J. THORACIC SURG. **22**: 88-93, 1951.
26. Philps, F. R.: The Identification of Carcinoma Cells in the Sputum, Brit. J. Cancer **8**: 67-96, 1954.
27. Umiker, W.: Cytology in Bronchiogenic Carcinoma, Am. J. Clin. Path. **22**: 558-563, 1952.
28. Vincent Memorial Hospital: The Cytologic Diagnosis of Cancer, Philadelphia, W. B. Saunders Co., 1950, 229 pp.
29. Wandall, H. H.: A Study of Neoplastic Cells in Sputum as a Contribution to the Diagnosis of Lung Cancer, Acta chir. scandinav. supp. **91**: 1-143, 1944.
30. Watson, W. L., Cromwell, H., Craver, L., and Papanicolou, G. N.: Cytology of Bronchial Secretions, J. THORACIC SURG. **18**: 113-122, 1949.
31. Weiss, A. G.: Le diagnostic histologique des cancers bronchiques par biopsies et aspirations endobronchiques, Strasbourg Medical **3**: 410-412, 1952.
32. Woolner, L. B., and McDonald, J. R.: Cytologic Diagnosis of Bronchiogenic Carcinoma, Am. J. Clin. Path. **19**: 765-769, 1949.
33. Woolner, L. B., and McDonald, J. R.: Cytology of Sputum and Bronchial Secretions: Studies on 588 Patients with Miscellaneous Pulmonary Lesions, Ann. Int. Med. **33**: 1164-1174, 1950.

THROMBOSIS OF THE PULMONARY ARTERY COMPLICATING A CASE OF PULMONARY TUBERCULOSIS

VIKING OLOV BJÖRK, M.D., AND ÅKE NORHAGEN, M.D.
STOCKHOLM, SWEDEN

IN CASES of pulmonary tuberculosis, the arterial branches close to the tuberculous lesions are sometimes found thrombosed. Occasionally a segmental artery is found thrombosed, but only once in a series of 500 resections for pulmonary tuberculosis was the main pulmonary artery found almost completely occluded. After excision of the thrombosed area of the pulmonary artery and a left upper lobectomy with decortication of the lower lobe, the oxygen uptake increased from 4 to 15 per cent on the left side, and an angiography showed a patent pulmonary artery.

CASE REPORT

A 36-year-old man developed a large tuberculous cavity in the left upper lobe in 1946 and was treated with an artificial pneumothorax. There was a spread to the right side with a cavity in the superior segment of the right lower lobe in 1948. A good regression occurred on the right side. On the left side, the pneumothorax was abandoned in 1953 with considerable displacement of the mediastinum to the left. The cavity was still visible in the left upper lobe. There was no bronchial stenosis. Bronchospirometry showed 4 per cent oxygen uptake, 7 per cent of the vital capacity, and 2 per cent of the minute ventilation on the left side.

A two-stage procedure was performed in January, 1953, with a preliminary 5-rib thoracoplasty with apicolysis (Fig. 1). Three months later, the left side of the chest was opened through the bed of the sixth rib. The lung was mobilized in the extrapleural plane, and the lower lobe was decorticated. The segmental arteries to the left upper lobe were dissected free, and divided. The most proximal segmental artery to the anterior segment was thrombosed. As the main pulmonary artery at this level was felt firm on palpation, it was dissected free centrally to the bifurcation and opened between clamps. A 2 by 2 by 2 cm. large thrombus was found adherent to the wall of the pulmonary artery around the orifice to the anterior segmental artery. The opposite wall of the pulmonary artery was free. The lumen was 90 per cent occluded. The wall of the pulmonary artery containing the thrombus was excised and a continuous suture of silk was applied (Fig. 2). The left upper lobe was removed, and immediately after the operation, bronchospirometry showed 11 per cent oxygen uptake on the left side. The preoperative value had been only 4 per cent.

Microscopic examination revealed a normal wall of the pulmonary artery and an organized thrombus.

The patient made an uneventful recovery. One year after the operation, the patient showed a negative guinea pig test on sputum and gastric washings, and had an x-ray of the chest (Fig. 3) very similar to the preoperative one (Fig. 1). Angiography showed a normal left pulmonary artery. Bronchospirometry showed 15 per cent oxygen uptake, 16 per cent minute ventilation, and 17 per cent vital capacity on the left side.

From the Sabbatsberg Hospital: Surgeon-in-chief: C. Crafoord, M.D., Professor, Physician-in-chief: S. Björkman, M.D.
Received for publication Jan. 8, 1955.

DISCUSSION

A slow rate of blood flow will increase the risk of thrombosis. In this case, the left lung was atelectatic during one period of the pneumothorax treatment. The decreased blood flow through the left lung may then have facilitated the thrombus formation originating from a segmental artery. Before the operation, only 2 per cent of the minute ventilation was on the left side. Therefore, a thrombosis of the left pulmonary artery was not expected

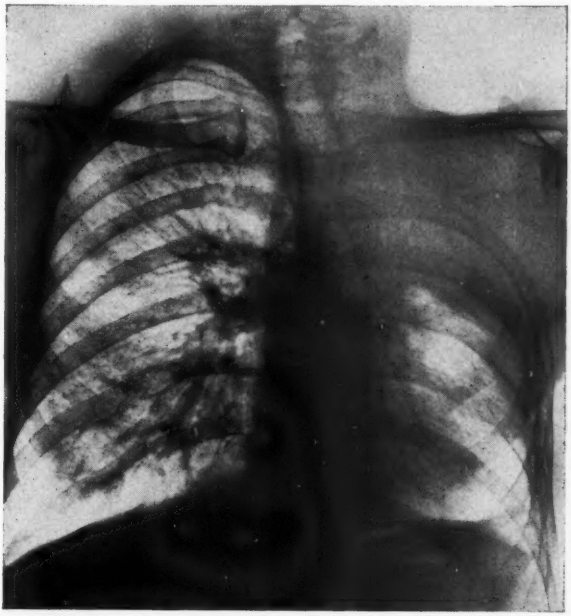


Fig. 1.—X-ray of the chest in March, 1953, before the operation.

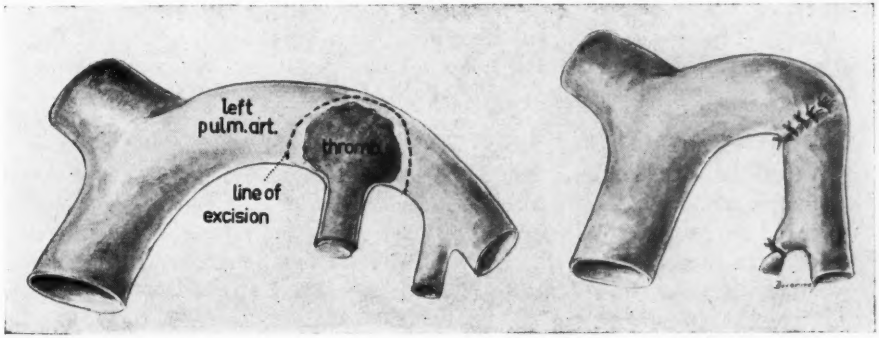


Fig. 2.—Diagram of the thrombus in the left pulmonary artery, the excision, and the vascular repair.

preoperatively. As ventilation increased after the operation from 2 to 16 per cent and the oxygen uptake from 4 to 15 per cent, the decortication played an important part in the improvement of function.

Such an improvement would, however, never have been possible without the excision of the thrombus. After the operation, there was no thrombosis in the suture line.

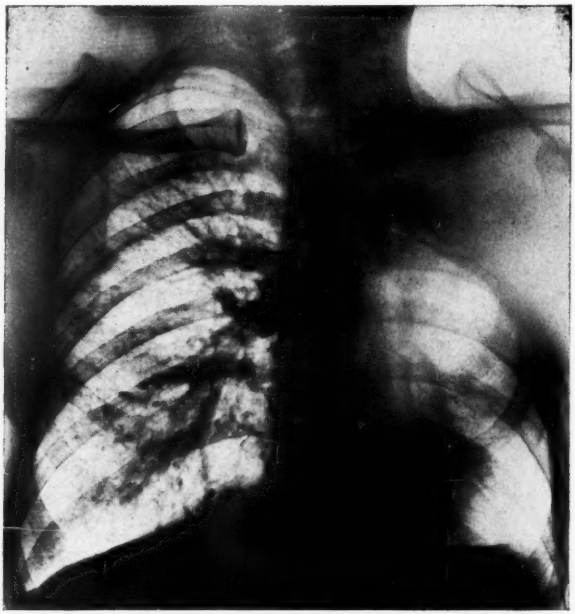


Fig. 3.—X-ray of the chest in March, 1954, one year after the operation.

In cases with practically no oxygen uptake in one lung, a thrombosis of the pulmonary artery may be detected by angiography. At operation, the pulmonary artery may easily be palpated and, if something unusual is found, it should be opened as in the case described. Excision of a thrombus, with the adjacent pulmonary arterial wall and a vascular repair, can evidently be done without recurrent thrombosis in spite of a comparatively small flow.

SUMMARY

A case is described in which a left upper lobectomy, left lower lobe decortication, and excision of a thrombus formation in the left pulmonary artery improved the oxygen uptake from 4 to 11 per cent. One year later the oxygen uptake was 15 per cent on the left side, and the left pulmonary artery was patent.

REFERENCE

Björk, V. O.: Circulation Through an Atelectatic Lung in Man, J. THORACIC SURG. 26: 533, 1953.

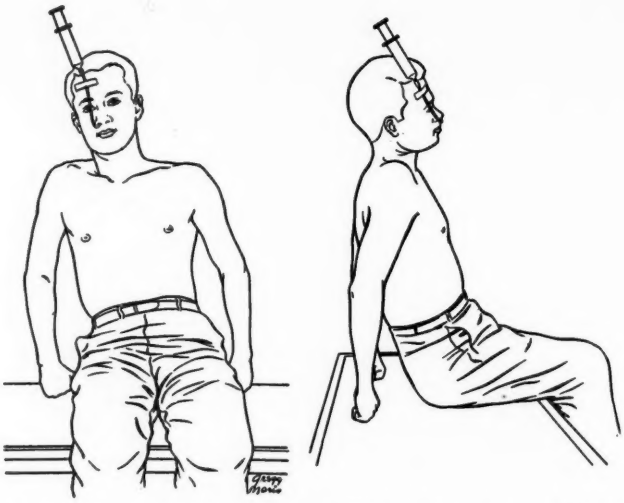
TECHNIQUE OF BRONCHOGRAPHY

S. W. French, III, Colonel, MC, USA
San Francisco, Calif.

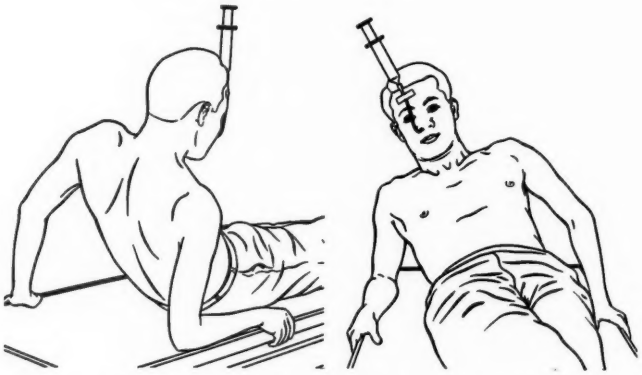
THE following line drawings illustrate the various positions which the author has successfully used for several years in bronchography. This method is simple, can be performed quickly without the aid of fluorscopy, and uniformly produces excellent bronchograms.

Topical 5 per cent cocaine anesthesia is used, the pharynx being sprayed with an atomizer, following which the internal division of the superior laryngeal nerve is cocainized in the anterior portion of the piriform sinus with a Jackson forceps containing cotton saturated with the anesthetic agent. A catheter is then inserted through the nose into the trachea under direct vision by use of a laryngeal mirror. Following insertion of the catheter, a total of 4 c.c. of cocaine is instilled into the trachea through the catheter, with the patient leaning first to the right and then to the left in order to complete the anesthesia of the tracheobronchial tree.

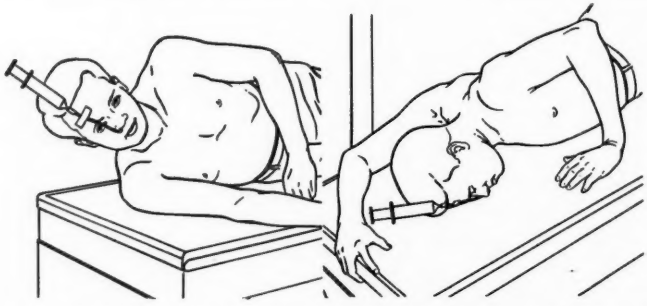
From the Thoracic Surgical Service, Letterman Army Hospital, San Francisco, Calif.
Received for publication Feb. 3, 1955.



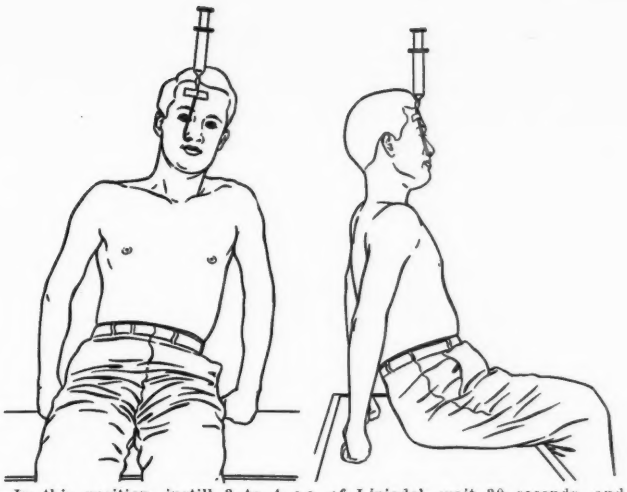
Position 1.—Frontal and lateral views. In this position, instill 6 c.c. of Lipiodol, wait 30 seconds, and proceed to Position 2.



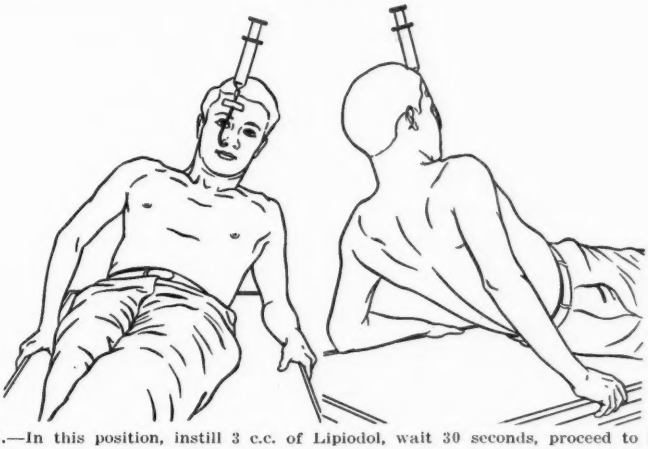
Position 3.—Instill 3 c.c. of Lipiodol, wait 30 seconds, and proceed to Position 4.



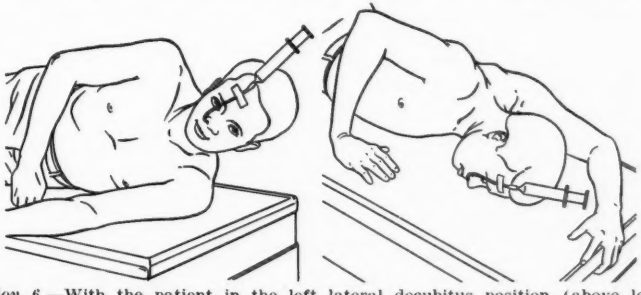
Position 5.—With the patient in the right lateral decubitus position (above left), instill 3 c.c. of Lipiodol and wait 30 seconds. The patient is then turned to the right anterior oblique position, as in the figure above, the table depressed to a 30 degree angle, and held in this position for 30 seconds.



Position 2.—In this position, instill 3 to 4 c.c. of Lipiodol, wait 30 seconds, and proceed to Position 3.



Position 4.—In this position, instill 3 c.c. of Lipiodol, wait 30 seconds, proceed to Position 5.



Position 6.—With the patient in the left lateral decubitus position (above left), instill 3 c.c. of Lipiodol and wait 30 seconds. The patient is then turned to the left anterior oblique position, as in the figure above, the table depressed to a 30 degree angle, and held in this position for 30 seconds.

At this time posteroanterior and right and left anterior oblique films are taken with the patient upright. Lateral films may be taken if so desired.

THE HISTORY OF THE DEVELOPMENT OF THE NEGATIVE DIFFERENTIAL PRESSURE CHAMBER FOR THORACIC SURGERY

HERBERT WILLY MEYER, M.D.,
NEW YORK, N. Y.

IN 1953 at the San Francisco meeting of the American Association for Thoracic Surgery, Dr. Robert M. Janes, in his Presidential Address, spoke about the negative pressure chamber. He stated that the only one in existence in America in 1922 was located at the Lenox Hill Hospital in New York. Willy Meyer, who designed it, had combined the principles of negative pressure of Sauerbruch and the principles of positive pressure of Brauer.

It occurred to me at that meeting that some of the members and visitors might not have heard about the negative chamber, or understood what was meant by the term "negative pressure chamber." Therefore, I thought a brief historical sketch might be timely and possibly of interest for those whose interest in thoracic surgery followed the birth, life, and death of the negative pressure chambers.

It seems especially proper at this time to honor the memory of Ferdinand Sauerbruch, as it was fifty years ago in 1904 that he discovered the method by which he could safely open the pleural cavity of dogs under negative differential pressure.

The danger of thoracic surgery in those days was the occurrence of pneumothorax upon opening the pleural cavity. This word was coined by an English physician named Hewson. In 1902 there was no reliable and consistently practical method of overcoming this pneumothorax.

Sauerbruch became an assistant of Professor von Mikulicz at the Surgical Clinic in Breslau, Germany, on Oct. 1, 1903, when he was only 28 years of age.

Professor von Mikulicz was greatly interested in the development of a method of making thoracic surgery feasible. He encouraged and stimulated young Sauerbruch to investigate this problem. Sauerbruch published his autobiography *Das War Mein Leben* in 1951. In it, he tells the story of awakening one night and conceiving the idea of how to overcome the deadly pneumothorax. He suddenly realized what had to be done in his experimental work on dogs to prove his theory. It was purely a physiological problem. It was a question of negative differential pressure. The apparatus he built and developed in 1904 proved successful. He had thereby discovered a safe method of performing surgery within the thorax.

Received for publication Jan. 13, 1955.

Sauerbruch's first research and construction of an apparatus began in October, 1903. This was a primitive apparatus (Fig. 1). He operated upon several dogs successfully. However, the first time he tried to demonstrate the apparatus to von Mikulicz, by opening the pleural cavity of a dog under negative pressure, there was a leak in the rubber cuffs and the negative pressure was lost. The lung of the dog collapsed due to pneumothorax and the dog died, to the dismay of both Sauerbruch and von Mikulicz. Sauerbruch had purposely opened both pleural cavities.

The second apparatus was constructed of wood (Fig. 2). There was a glass top. Two persons could work within this wooden box for two hours at a time but no longer on account of the intense heat that developed inside the cabinet. The third larger box contained 14 cubic meters of air space. Five persons could be within this chamber (Fig. 3).

Professor von Mikulicz invited his young assistant Sauerbruch to be his guest at the following meeting of the German Surgical Society in Berlin on April 6, 1904. Sauerbruch read his paper and demonstrated the apparatus. They had performed 78 operations on dogs. Thoracotomy had been completed without mortality. The operations had been performed by von Mickulicz with Sauerbruch in control of the negative pressure. They had found that minus 10 mm. Hg of negative pressure sufficed to prevent pneumothorax. This was equivalent to operating at an altitude of 300 meters. Surgeons and assistants could easily stand this degree of negative pressure. Sauerbruch stated at that time that it was his opinion that human beings could likewise undergo thoracic surgery if negative differential pressure was employed.

It is of historic interest that Willy Meyer, the Founder of the American Association for Thoracic Surgery, visited von Mikulicz and Sauerbruch in Breslau in the summer of 1904. Sauerbruch invited Willy Meyer to be inside the negative chamber and witness a transthoracic resection of the esophagus on a dog. Willy Meyer reported this fascinating experience before the New York Surgical Society on Dec. 14, 1904. His paper was published in the *Annals of Surgery* 41: 667-685, 1905.

Following the meeting of the German Surgical Congress, von Mikulicz had an even larger negative chamber built. This one was adequate for operations on human beings. At first 13 operations on the esophagus were performed on dogs in this chamber. He then felt that they were ready for surgery on human beings under negative pressure. The first patient had a carcinoma of the esophagus. The patient died during the operation. The second operation in the negative chamber was for the removal of a tumor of the mediastinum. This patient survived.

It was at this time that several positive pressure apparatuses were constructed in other clinics in Europe. This fact quickly followed Sauerbruch's presentation before the German Surgical Congress. Brauer of Heidelberg constructed a mask-type apparatus. Von Mikulicz had previously employed

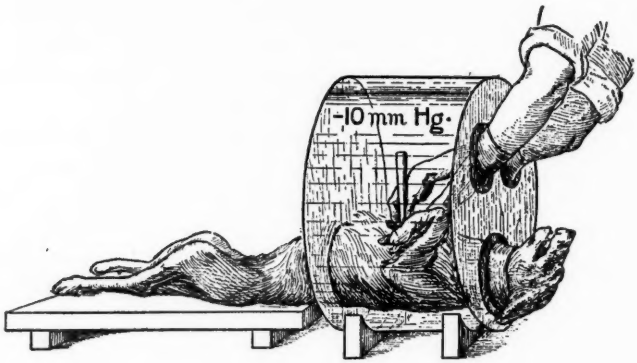


Fig. 1.—Sauerbruch's original primitive apparatus for negative pressure. (Fig. 1-3 copied from Sauerbruch's early articles.)

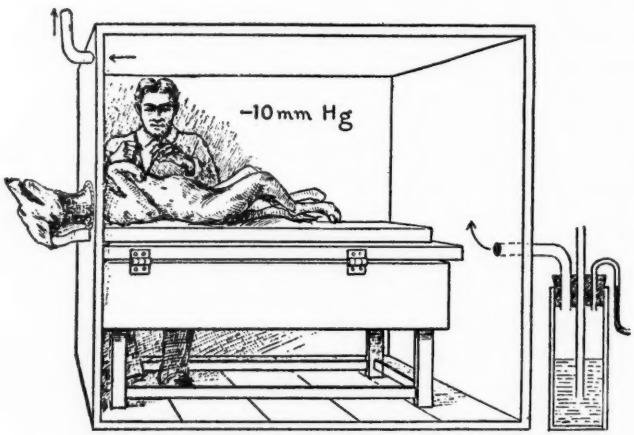


Fig. 2.—Sauerbruch's first wooden chamber designed for operations under negative pressure.

a somewhat similar type of apparatus, but found it wanting and greatly preferred to work under negative pressure. These positive and negative pressure apparatuses were physiologically diametrically opposite in principle. This brought forth discussion and arguments as to which method was preferable for surgery on sick patients. Improvements in positive pressure apparatuses were made by such men as Engelken, Tiegel, Brat-Schmieden, Seydel, Karewski, and Robinson.

Physiologists and surgeons had long before this time overcome pneumothorax in animal experimentation by blowing air into the trachea and then sucking it out. Matas and others were pioneers in this work in the late nineteenth century. Sauerbruch, however, had greatly advanced thoracic sur-

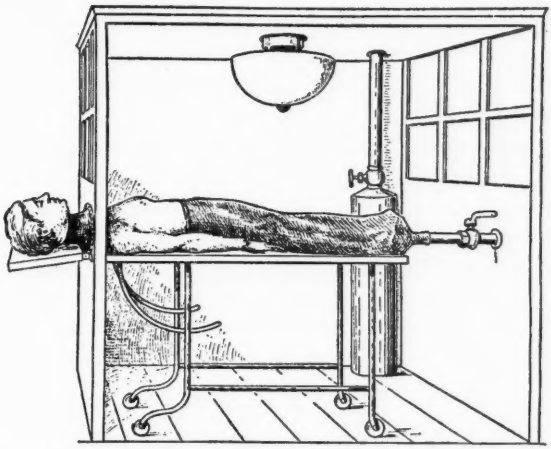


Fig. 3.—Early chamber used at the Breslau Clinic for operations under negative pressure. Note that lower portion of the body of the patient is within rubber bag connected with outside atmospheric pressure so that only the chest portion was under negative pressure. It was within this chamber that Willy Meyer witnessed operation on esophagus of dog in 1904.

gery by developing the negative differential pressure chamber. It made normal administration of general anesthesia possible. There was, however, no chamber or apparatus in which it was possible to determine whether negative or positive differential pressure was the preferable method for the sick patient.

In 1905, while this fascinating, new research work was progressing, Professor von Mikulicz died of carcinoma. This tragedy interrupted this important work. Professor Garré replaced von Mikulicz in Breslau. Sauerbruch was transferred to Greifswald under Professor Friederich. In 1907, both Friederich and Sauerbruch were moved to Marburg, where surgery under negative pressure was resumed.

In 1908, the Section on Surgery of the American Medical Association invited Sauerbruch to come to the United States to present a paper and demonstrate the negative chamber. Sauerbruch accepted this invitation. He arrived in New York City and brought along the negative chamber. Willy Meyer met him at the pier in New York and acted as his host. The American Medical Association met in Chicago that year. The negative chamber was shipped to Chicago. Sauerbruch read his paper and demonstrated the negative chamber.

Sauerbruch told Willy Meyer in Chicago that he did not intend to take the negative chamber back to Germany. He offered to leave it with Willy Meyer in New York so that Willy Meyer could do some experimental work in thoracic surgery on dogs. Thereupon Willy Meyer asked Sauerbruch to consent to operate upon a dog in the chamber while he was in New York City before he sailed for Germany.

For the authenticity and completeness of the story that follows, I am indebted to Dr. Thomas Rivers, Director of the Rockefeller Institute for Medical Research in New York, and to Mr. E. B. Smith, the present Business Manager of the Institute. They kindly permited me to review some of their old records of those exciting days.

On May 29, 1908, Willy Meyer wrote to Dr. Simon Flexner, at that time the Director of the Rockefeller Institute, and asked for permission to erect the negative chamber at the Institute so that Sauerbruch could operate upon a dog before he sailed for Germany. Inasmuch as Willy Meyer was not a member of the Scientific Staff of the Rockefeller Institute, it was most gracious on the part of the Directors to grant this permission. Therefore, Sauerbruch operated upon a dog's lung under negative differential pressure on the morning of June 11, 1908, at the Rockefeller Institute. Willy Meyer assisted Sauerbruch at this operation. Among invited guests were the heads of the various departments of the Rockefeller Institute. They were Drs. Samuel Meltzer, the first President of the American Association for Thoracic Surgery, Alexis Carrel, E. L. Opie, and Dr. Levene. Following this operation, the chamber was dismantled and stored in the basement of the Institute.

Dr. Flexner thereupon kindly made arrangements so that Willy Meyer could start research work in this entirely new field of thoracic surgery at the Rockefeller Institute. Willy Meyer, however, had to pay for the dogs and also engage an attendant for the care of the dogs, and pay his salary. The Institute allotted him space for the erection of the chamber.

During the ensuing summer of 1908, Willy Meyer asked his brother, Julius Meyer, a mechanical engineer by profession, to tour Europe and visit every clinic where work was being done in thoracic surgery. All types of positive pressure apparatuses and the negative chamber were studied.

Willy Meyer had already decided to build his own chamber in which he could evaluate the pros and cons of negative differential pressure and positive differential pressure. The basic plan of action and specifications were:

1. To construct an apparatus in which any operation could be performed without moving the patient, whether negative or positive pressures were employed. The change from one pressure to the other had to be accomplished quickly.

2. There should be no change of position of the patient, surgeons, and anesthetist during the operation.

3. The administration of general anesthesia was to be a simple procedure under either negative or positive pressure.

4. The operation was to be performed under lower barometric pressure than the prevailing atmospheric pressure existing at the time of the operation.

Julius Meyer returned from Europe in September, 1908. After many conferences between the brothers, work was started on a positive pressure

chamber. This work was accomplished with the great aid of Mr. Robert Kny, the head of the Kny-Scheerer Surgical Instrument Company in New York. The factory was situated in New York City.

The capacity of the first chamber was 80 cubic feet. This chamber was large enough to comfortably hold two anesthetists. It had an antechamber lock division with doors, permitting change of pressure from positive to atmospheric pressure so that one of the anesthetists could leave the positive pressure chamber at any time. An adjustable guillotine partition with large rubber cuff surrounded the patient's neck for airtight closure. By means of motor pumps and valve action the degree of positive pressure was easily regulated. Atmospheric pressure could be easily changed to 10 or 15 mm. Hg positive pressure. Artificial respiration or inflation of the lung could be started by the simple control of the valve action. This allowed the lung to

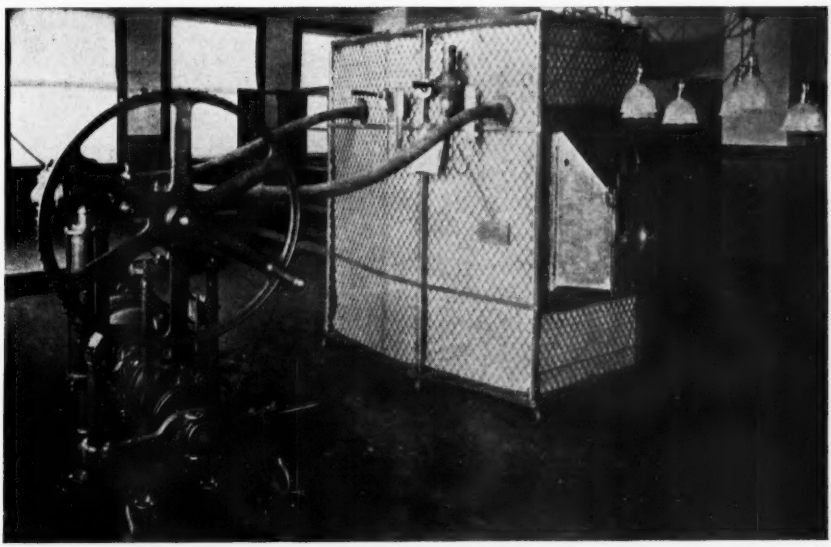


Fig. 4.—First positive pressure chamber of Willy Meyer used at the Rockefeller Institute for Medical Research for experimental surgery on dogs. Note positive pressure electric pump and emergency hand-geared pump in case of electric failure.

collapse and also to expand in a way similar to that with present-day intratracheal anesthesia with controlled respiration. This chamber was completed by the end of 1908. It was transferred to the Rockefeller Institute in January, 1909 (Fig. 4). Experimental surgery on dogs was started at that time. The records of the Institute show that the cost of a dog was 35¢ at that time. Mr. Smith tells me that today a dog costs $6.50.

Every Tuesday and Friday afternoon were set aside by Willy Meyer to go to the Rockefeller Institute for experimental surgery on dogs on the lungs, esophagus, and the heart. As a boy of 12 years of age, I was permitted

to accompany my father on Friday afternoons after school hours. I either sat inside the positive chamber with the anesthetist and learned about anesthesia, or I stood outside and observed operations on the intrathoracic organs. Sometimes I was allowed to handle the valves that regulated the positive pressure. Therefore, my personal interest in thoracic surgery extends over a period of 47 years.

After four weeks of experimental work, the positive chamber was dismantled and moved to the German Hospital, now the Lenox Hill Hospital. Early in 1909, the first operation on a human being was performed on the lung of a child. This positive pressure chamber was dismantled, transported, and erected four times within the following six months. It could be dismantled within a few hours and erected within a day. In June of 1909, the chamber was transported to Philadelphia. It was demonstrated at the Jefferson Medical College Hospital at the time of the annual meeting of the American Surgical Association in Philadelphia.

A second positive pressure chamber replaced the first at the Rockefeller Institute. Experimental thoracic surgery on dogs was continued.

In the meantime the Universal Negative Pressure Chamber was being constructed at the Kny-Scheerer factory. This chamber contained 1,000 cubic feet of air. Four silent muffled suction pumps sucked the air out of this large chamber. Negative pressure was obtained by regulating the inflow of outside air into the chamber through a large inflow pipe whose diameter was regulated by valve action. The negative pressure could be brought from atmospheric pressure to a differential of minus 15 to minus 18 mm. Hg within a few moments. It was quickly found that about minus 7 to minus 8 mm. Hg was the ideal negative pressure for thoracic surgery.

A positive pressure chamber had been placed at the far end, inside the negative chamber. The head of the patient and the two anesthetists were inside this smaller chamber. The body of the patient, the surgeon, his assistants, the instrument nurses, visitors, and engineer to control the valves were inside the larger negative pressure chamber. All in all, as many as 15 persons could be inside the larger chamber. If desired, therefore, 17 persons could be inside the Universal chambers, besides the patient.

This Universal Negative Chamber was brought to the Rockefeller Institute in May of 1909. On May 7, 1909, the first operation was performed on a dog. This operation was a pneumonectomy (Figs. 5 and 6).

One can readily see the advantages of the Universal Chamber. When there was minus 7 mm. Hg negative pressure in the chamber, the pleural cavity could be opened without collapse of the lung because the dog was breathing normal atmospheric pressure which was inside the smaller chamber. This could be interpreted as if the mouth of the dog were at sea level and the opened pleural cavity of the dog at an altitute of about 300 feet above sea level. If the differential pressure was to be changed, all that had to be done was to increase the pressure inside the smaller chamber to positive pressure

Fig. 5.

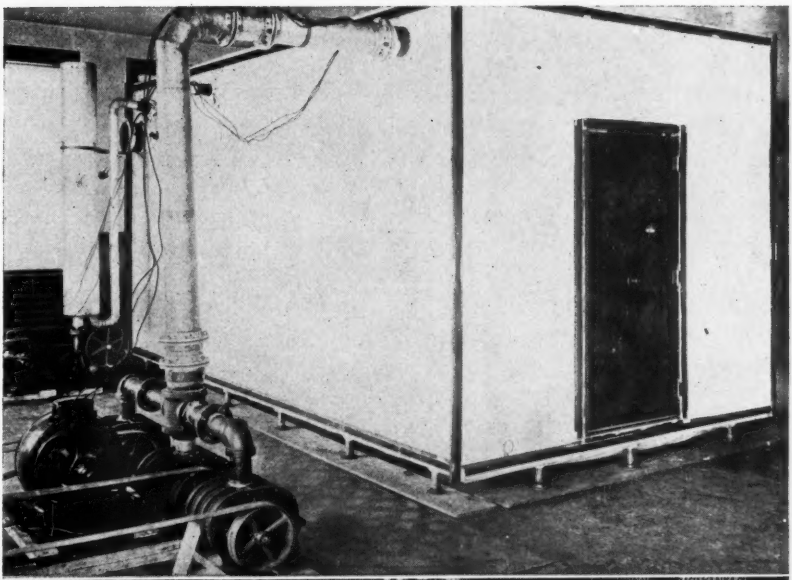


Fig. 6.

Fig. 5.—First experimental Universal Negative Chamber erected in the Rockefeller Institute for experimental surgery on dogs. Outer view. Note exhaust pumps in foreground and positive pressure pump in rear. Cover of chamber is balloon material.

Fig. 6.—Inner view of first Universal Negative Chamber. Note positive chamber within the negative chamber. Operating table for dog surgery in front of positive chamber. Note wire frame of chamber with balloon material outside.

Fig. 7.

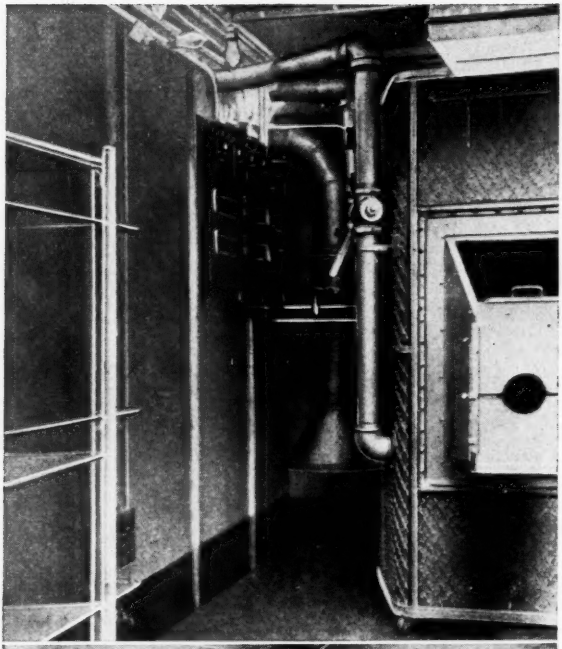


Fig. 8.

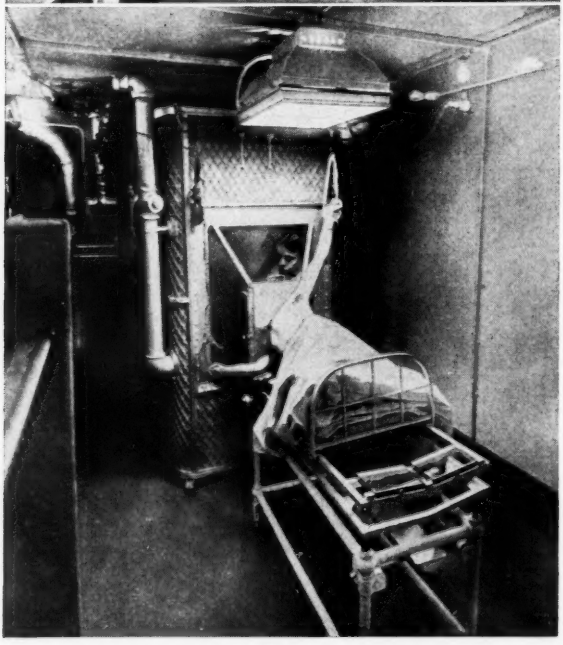


Fig. 7.—View of interior of Universal Negative Chamber as erected in the Pavilion for Thoracic Surgery at Lenox Hill Hospital. Note metal lining, instrument panel, valve handles for regulating negative pressure in rear, large inlet pipe and handle for positive pressure on inlet pipe in foreground. Electric control panel on side.

Fig. 8.—Operating table and patient in negative chamber. Anesthetist within positive chamber. Instrument stand in foreground on left.

and lower the negative pressure inside the larger chamber to atmospheric pressure. This change of pressures was possible within a few moments. Once the negative pressure in the larger chamber was at atmospheric pressure, the door to the outside could be opened and personnel could go in and out of the chamber. The ventilation of air inside the large and small chambers was excellent. The air was cool and there was a complete change of air in both chambers every two minutes.

Experimental surgery on dogs was continued at the Rockefeller Institute by Willy Meyer from the fall of 1908 until Dec. 31, 1913.

At the suggestion of the attorneys of the Rockefeller Institute, and of the Executive Committee of the Institute, Willy Meyer and Julius Meyer applied for a patent on the Universal Chamber. This patent was granted on Jan. 2, 1912. The patent issued was No. 1,013,800. It read: "Apparatus for Conducting Thoracic Operations." This patent was obtained in order to avoid possible priority interference with the use of the apparatus. Willy Meyer assigned the patent to the "People of the United States."

During this time, plans were instituted to build a Thoracic Surgery Pavillion at the German Hospital. Mr. J. Pierpont Morgan was one of the first contributors to the fund. This generous donation was given through the kindness of Dr. James Markoe, one of Willy Meyer's close friends. The Trustees of the German Hospital and many friends and patients of Willy Meyer also generously contributed to the building fund. The Department was completed and opened in April, 1911 (Figs. 7, 8, 9). It was the first and remained the only such specialized department for thoracic surgery in the United States. It housed the Universal Chamber, a positive pressure chamber, as well as other types of positive pressure apparatuses known at that time. During the experimental stage of the Universal Chamber at the Rockefeller Institute, a balloon-type rubber cloth enveloped the negative chamber. This was changed to a more durable metal covering when the chamber was erected at the German Hospital. The inside walls were also made smooth with thin metal. This made it possible to wash down the inside walls of the chamber for cleanliness.

I am proud and happy to mention that Dr. Carl Eggers, one of our past Presidents of the American Association for Thoracic Surgery, is probably the only living surgeon who frequently assisted Willy Meyer in the Universal Chamber at the German Hospital by being the anesthetist at many of the difficult operations. This was during the early and exciting days of thoracic surgery on human beings (Figs. 10, 11, and 12).

World War I broke out in 1914. It was very soon discovered on the battlefields, in the front-line hospitals, and in the base hospitals that these complicated apparatuses were not necessary for thoracic surgery. An efficient positive pressure anesthesia apparatus, properly employed, was all that was necessary. It was conclusively demonstrated that positive pressure was as efficient as negative pressure. It fulfilled the demands of the thoracic surgeon.

Fig. 9.

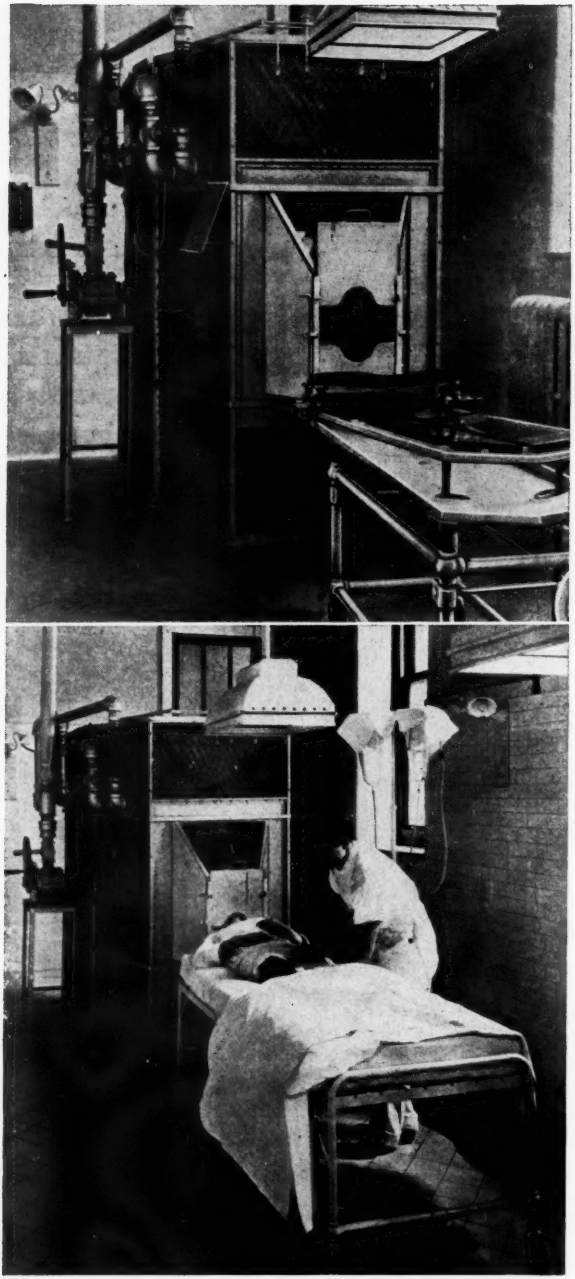


Fig. 10.

Fig. 9.—Positive chamber in Thoracic Pavilion at the Lenox Hill Hospital.

Fig. 10.—Photograph of patient on bed under positive differential pressure during post-operative treatment. Head of patient and nurse within positive chamber. Orderly and body of patient and thoracic cavity with free drainage of chest cavity outside under atmospheric pressure.

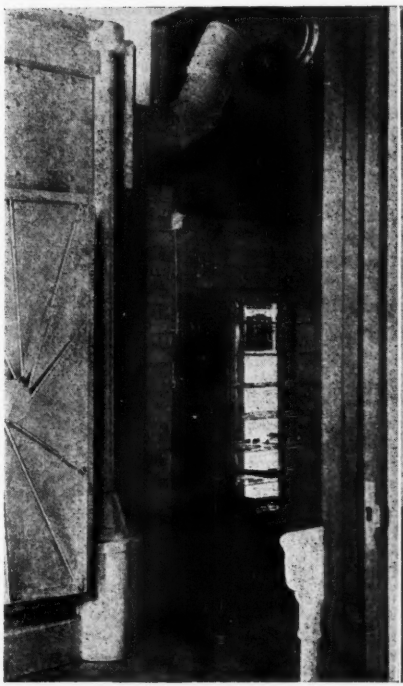


Fig. 11.

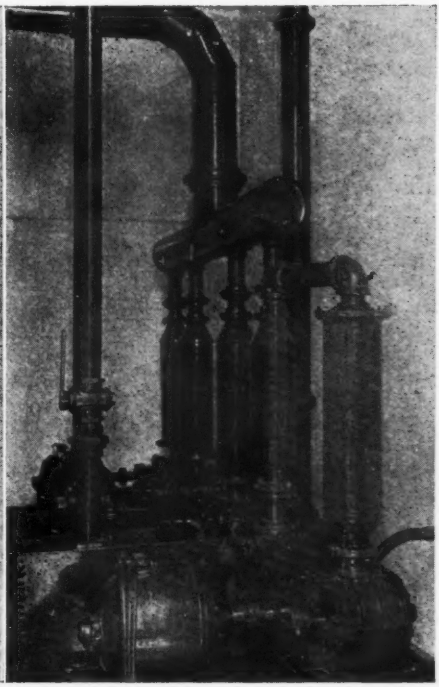


Fig. 12.

Fig. 11.—Vault type of metal door leading into Universal Negative Chamber at the Thoracic Pavilion in the Lenox Hill Hospital. Note metal outside covering and large exhaust pipe leading to exhaust motors in engine room.

Fig. 12.—Four muffled silent exhaust vacuum pumps and one positive pressure pump in engine room of the Thoracic Pavilion of the Lenox Hill Hospital.

In 1923, the Lenox Hill Hospital needed more space for an expanding x-ray department. The Trustees of the Hospital decided that the Thoracic Pavilion space would be ideal for this department. Therefore, the Universal Negative Chamber—the only one in existence in the world—had to be dismantled. Willy Meyer offered it to the Rockefeller Institute on June 19, 1923, for further experimental work. The offer had to be declined, also on account of lack of space. The Universal Chamber and the two positive pressure chambers were, therefore, dismantled and the metal was sold by the Hospital as scrap metal. I have often thought that it was a pity that this unique and ingenious Universal Chamber was not offered to the Smithsonian Institute in Washington, D. C. It was a brilliant conception of an apparatus that very closely simulated the normal physiology of the thoracic cavity. It certainly was more physiological than any positive pressure method. If a negative chamber were available today, it would be fascinating and interesting to speculate, experiment, and see whether it might not be of real value in the surgery of modern heart lesions, especially in the very ill cardiac patient.

All honor therefore to the memory of those great pioneers in thoracic surgery and to the contributions which they made in those early days of this fascinating chapter of surgery.

REFERENCES

Meyer, Willy: Transthoracic Resection of the Lower End of the Esophagus in a Dog, Ann. Surg. **41**: 667-685, 1905.
Bemerkungen zur Weiterentwickelung des Druckdifferenz-Verfahrens für Intrathorakale Operationen. Aus der Festschrift zur Vierzigjahrigen Stiftungsfeier des Deutschen Hospitals in New York, 1909.
Aus der Festschrift zur Vierzigjahrigen Stiftungsfeier des Deutschen Hospitals in New York, 1909.
The New Operating Pavilion for Thoracic Surgery at the German Hospital, M. Rec. New York **79**: 1079-1084, 1911.
On Drainage After Intrathoracic Operations With Special Reference to the Esophagus, Ann. Surg. **56**: 100-111, 1912.
Post-Operative Thoracic Drainage, Ann. Surg. **68**: 156-168, 1918.

Erratum

The title of the article by William G. Childress, M.D., and George C. Adie, M.D., which appeared in the May, 1955, issue of the JOURNAL, pages 480-487, should be "Recurrent Plasmacytoma of the Mediastinum" rather than "Recurrent Plasmacytoma of the Lung."

Announcements

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Thirty-sixth Annual Meeting of the American Association for Thoracic Surgery will be held May 7, 8 and 9, 1956, in Miami Beach, Florida. Headquarters will be at the Hotel Fontainebleau.

Requests for Hotel Reservations

These should be mailed directly to Mr. Jack Slone, Director of Sales, Hotel Fontainebleau, Miami Beach, Florida. Please mention this Association, the type of accommodation desired, the date and approximate hour of arrival and departure. If accommodations are desired elsewhere in Miami Beach, please communicate directly with the hotel of your choice.

Thoracic Surgical Forum

The Thoracic Surgical Forum will be continued as a special session at the 1956 meeting. The Forum is primarily for the presentation of short papers on current thoracic research, experimental problems, anatomical studies and modified or new surgical techniques. The inclusion of any considerable amount of clinical material in these reports makes the choice more difficult and the Program Committee reserves the right to reject such papers, or to suggest their transferral to the Regular Program.

Papers at this session will be limited to ten minutes, including the showing of lantern slides or other illustrative material. At the discretion of the President, three minutes may be allowed as the maximum discussion for each paper.

All Thoracic Surgical Forum papers will be published together in one issue of the JOURNAL. Maximum length: 3000 words without illustrations. If illustrated, an appropriate number of words must be subtracted for each cut used.

Abstracts for Papers

Abstracts for the presentation of all papers at the 1956 meeting must be received on or before Dec. 15, 1955, otherwise they will not be considered by the Program Committee.

Abstracts should be labeled "For Thoracic Surgical Forum," or "For Regular Program." The abstracts should contain from 200 to 250 words and accurately reflect the contents of the completed paper.

Five, repeat, five copies of *each* abstract must be sent to the Secretary of the Association, Dr. Paul C. Samson, 3959 Happy Valley Road, Lafayette, California. They should not be sent to the Editor.

Those on the program are reminded that papers presented at the meeting *must* be handed to the secretary immediately after their presentation. If they are not ready at that time there is a chance that they will not be published in the JOURNAL OF THORACIC SURGERY.

Motion Picture Session

Provisions have been made to show a limited number of motion pictures to be selected on a competitive basis. *The films themselves,* together with descriptive material concerning length of presentation, etc., must be received by Dr. Julian Johnson, University Hospital, 3400 Spruce St., Philadelphia 4, Pa., before Dec. 15, 1955.

It is planned to run the motion pictures in a smaller room at the same time as the scientific sessions. If the films are well labeled, it will not be necessary for the author to be present for comment.

Applications for Membership

Applications for Associate Membership in the Association must be received by the Membership Committee not later than Dec. 15, 1955, otherwise, the applications will be deferred for consideration until the 1957 meeting.

Applicants must be sponsored by three Active or Senior Members of the Association. In addition to the signatures on the application form, the sponsors will forward a *separate* letter concerning the applicant directly to:

Dr. O. T. Clagett
Chairman of the Membership Committee
Mayo Clinic
Rochester, Minn.

Sponsors are reminded that *new* letters of recommendation must be forwarded to the Membership Committee should their applicants be held over for reconsideration a second year.